Vol. 38 MAY, 1951 No. 5

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THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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Vol. 38, No. 5, May, 1951. The Journal of Pediatrics is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: The United States, its Possessions and Pan-American Countries, $10.00 a year; Canada and other foreign Countries, $11.00 a year. Entered as Second-class matter June 29, 1932, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

The Journal of Pediatrics

VOL. 38 MAY, 1951 No. 5

Original Communications

TONSILLECTOMY AND POLIOMYELITIS

I. STUDIES ON INCIDENCE IN 1949

MORRIS SIEGEL, M.D., MORRIS GREENBERG, M.D., AND M. CATHERINE MAGEE, M.D.
NEW YORK, N. Y.

IN RECENT years, attempts have been made to determine the incidence of poliomyelitis following tonsillectomy. The problem is beset with difficulties stemming from the low incidence of the disease, poor reporting, incomplete data on the population at risk, and several variables, such as age, monthly incidence, and time of operation, that require correction.

Many of the reported studies have been made by otolaryngologists who obtained their data from surveys of patients, physicians, hospitals, and health departments. The results of such surveys have pointed to the rarity of poliomyelitis following tonsillectomy.[1-13] However, they have not proved that poliomyelitis following tonsillectomy is as uncommon as the prevailing incidence of poliomyelitis in the general population.[14, 15] On the other hand, other investigators have reported evidence of an increase in the incidence of poliomyelitis following operation.[16, 17] Where many operations were performed during an outbreak, the incidence in tonsillectomized individuals was found to be several times greater than in the general population.[17] In addition, experimental evidence of an increase in susceptibility to poliomyelitis of cynomolgus monkeys following tonsillectomy has been reported.[18]

Because of the conflicting reports, a study was undertaken on the relationship of poliomyelitis to tonsillectomy. Two aspects of the problem were investigated, one on the incidence, the other on the frequency of the bulbar type among cases of poliomyelitis following tonsillectomy. A report on incidence is made below.

METHOD

Data were obtained during 1949, when New York City experienced its third largest outbreak of poliomyelitis.[19] A total of 2,446 cases and 179 deaths was reported during the year in a population of approximately 8 million. The case rate was 30.0 per 100,000 and the case fatality 7.3 per cent.

The reported cases included paralytic and nonparalytic forms of poliomyelitis. The diagnosis of poliomyeli-

From the Bureau of Preventable Diseases, New York City Department of Health.

tis was based on at least three of the following findings: fever, stiff neck or back, flaccid paralysis, and 10 to 500 white cells per cubic millimeter of spinal fluid obtained in the acute stage. Those with flaccid paralysis or muscle weakness of spinal or bulbar origin were considered as paralytic cases, all others as nonparalytic. The clinical data were recorded by departmental diagnosticians and reviewed by us.

Information on the removal of tonsils and adenoids in reported cases of poliomyelitis was obtained by a diagnostician who visited all patients within twenty-four hours after notification by the private physician, and by an epidemiologist who visited the home within one to two weeks. The exact date and place of operation were checked with the respective hospitals and surgeons.

At the end of the year the hospitals in New York City were asked to report by age group the monthly number of tonsillectomies* performed in 1949. Replies were received from all hospitals. They reported a total of 53,007 operations. The requested data on age and month of operation were given in 51,475 cases or 97.1 per cent of the total number reported. In the remaining 1,532 cases (2.9 per cent), reported by three hospitals, only the number of operations each month was known without reference to age group. In these cases, the monthly age distribution was assumed to be comparable to that observed in other hospitals.

Data on operations performed in private offices were not included in the present study because such information was not complete. As shown in Table I, twenty-three cases or almost a third of the reported cases of poliomyelitis in recently tonsillectomized individuals followed operations in private offices, and had to be excluded from studies on incidence since the population at risk in this category was unknown. Also excluded for the same reason was a case following operation in an out-of-town hospital. Thus, the present analysis was limited to cases of poliomyelitis occurring in 1949 following tonsillectomy performed in New York City hospitals during the same year. The experiences of past years were not examined, because the necessary hospital data could not be obtained.

*Refers to removal of tonsils or adenoids or both. We are indebted to the hospitals of New York City for making the data available.

RESULTS

A summary of the clinical forms of poliomyelitis reported after tonsillectomy in the group studied and in the group excluded from the study is shown in Table I.

TABLE I

PLACE OF OPERATION	TOTAL	TYPE OF POLIOMYELITIS			
		PARALYTIC		NONPARALYTIC	
		NO.	%	NO.	%
New York City Hospitals	50	36	72.0	14	28.0
Private offices and out-of-town	24	20	83.3	4	16.7
Total	74	56	75.7	18	24.3

The types of poliomyelitis following tonsillectomy in New York City hospitals were comparable to the types found in the group excluded from the report.

The size of the tonsillectomized population considered in the study is given in Chart 1 by age group and month of operation during 1949. The total

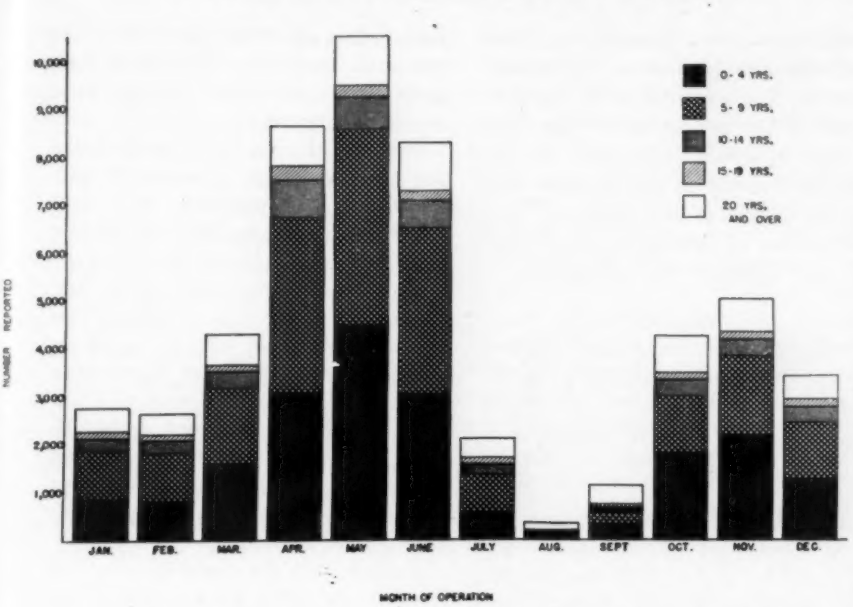

Chart 1.—Tonsillectomies reported by hospitals, New York City, 1949.

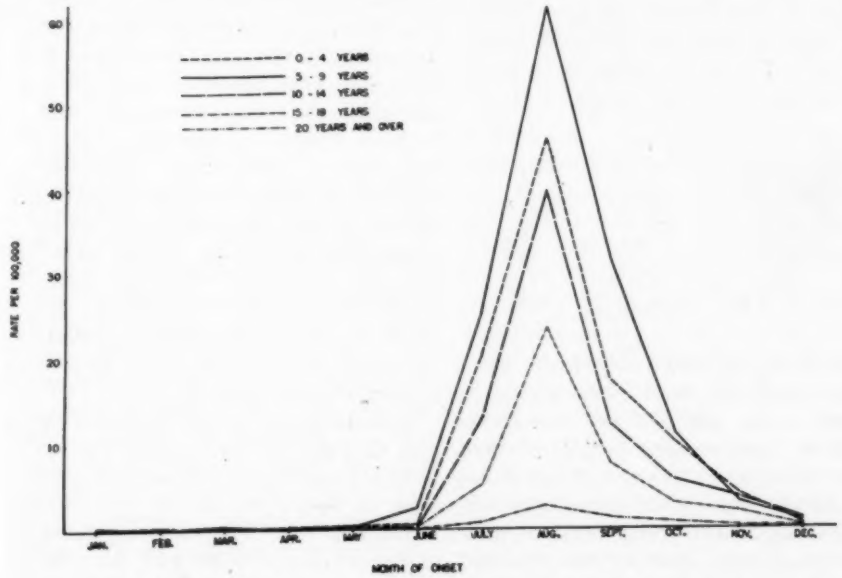

Chart 2.—Age specific rates of poliomyelitis by month of onset, New York City, 1949.

shown for the year was 53,007. There was considerable seasonal fluctuation, with the largest number of tonsillectomies in the spring before the onset of the epidemic, followed by the smallest number in the summer during the height of the epidemic. The distribution of operations by quarter-year periods is given in Table II.

TABLE II

PERIOD	NO.	%
January-March	9,601	18.1
April-June	27,353	51.5
July-September	3,516	6.7
October-December	12,537	23.7
Total	53,007	100.0

About 75 per cent of the operations were performed in the spring and fall, and 6.7 per cent in the summer. The monthly figures varied from 10,488 in May to 346 in August.

The number of tonsillectomized individuals also varied with age (Chart 1). Most of them were under 10 years of age. The actual numbers in each age group are shown in Table III.

TABLE III

AGE (YEARS)	NO.	%
0- 4	19,698	37.0
5- 9	19,809	37.3
10-14	4,329	8.2
15-19	1,792	3.5
20 and over	7,379	14.0
Total	53,007	100.0

Thirty-seven per cent of the persons operated upon were under 5 years of age and 37.3 per cent from 5 to 9 years, making a total of 74.3 per cent under 10 years of age. At 10 to 14 years of age there were 8.2 per cent, at 15 to 19, 3.5 per cent, and at 20 and over, 14.0 per cent. A seasonal fluctuation in number of operations performed was observed to varying degrees in each age group. It was somewhat more marked among those under 15 years of age than among older patients.

Some of the essential characteristics of the epidemic to which the tonsillectomized population was subjected were its seasonal character, trend, and age differences. Very few cases were reported during the first six months of the year. Indeed, there was no indication of the oncoming outbreak until July when there was a sharp rise in cases that continued to a peak in mid-August when a decline began. The decline continued through September, October, and November, and reached the mean nonepidemic base line in December.

Almost half the cases occurred in August and 85 per cent during the summer months of July, August, and September. October had 9 per cent of the cases, November 3.5 per cent, and December 1 per cent. Thus, the cumulative percentage for the second half of the year was 98.5. In the first half of the year, there were 1 per cent in June, about a quarter per cent in May, and a quarter per cent from January through April. The seasonal character and trend appeared to be comparable in each age group. However, the rates were uniformly highest in the 5- to 9-year age group, followed in descending order by those at 0 to 4, 10 to 14, 15 to 19, and 20 years and over (Chart 2).

A detailed method of bookkeeping was devised for determining the expected number of cases according to time of operation, month of occurrence, and age. For each age group the basic data consisted of the number of operations and the incidence in each month (Charts 1 and 2). As de-

scribed below, the number of operations multiplied by incidence in a specific age group gave the number of cases expected by age group, month of onset, month of operation, and interval between operation and onset.

By the methods employed, 38.6 cases of poliomyelitis were expected in the tonsillectomized group in 1949. Actually, 50 cases were reported, an increase of 11.4 cases or 29.5 per cent over the expected number.

The difference between the total number of cases expected and the total number observed was caused chiefly by the outcome in the 5- to 9-year age group, as shown in Chart 3 and in the tabulation of cases by age group in Table IV.

TABLE IV

AGE (YEARS)	OBSERVED	EXPECTED	DIFFERENCE
0- 4	15	14.2	+ 0.8
5- 9	32	21.1	+10.9
10-14	2	2.5	− 0.5
15-19	1	0.5	+ 0.5
20 and over	0	0.3	− 0.3
Total	50	38.6	+11.4

Most of the patients were under 10 years of age as anticipated from the many operations and high attack rate in this group. Few cases were expected or occurred in the older age groups. The difference at 5 to 9 years of age was about 50 per cent more in the observed than in the expected number of cases and was considered statistically significant.* In the other age groups little if any difference was noted in the number of cases observed and expected during the year. From this experience, therefore, it seems that the most vulnerable group to operation, as judged by the incidence of poliomyelitis in 1949, was the age group with the highest attack rate.

The distribution of cases by month of onset is shown in Chart 4. To determine the expected cases by month of onset, the incidence rate in each age group for a given month was multiplied by the total number of operations in the same age group prior to that month plus one-half the number of operations occurring in that month. The sum of the expected cases in each age group gave the total expected for all age groups for a given month. For example, the cases expected in July was equal to the age-specific rates in July multiplied by the cumulative number of operations in the respective age groups from January through June plus half of those in July.

The distribution of expected cases by month of onset paralleled the seasonal curves noted in Chart 2, weighted on the side of those under 10 years of age, because three-quarters of the operations were in this age group. In general, the trend of observed cases followed the expected epidemic pattern with a higher peak in August and slower rate of decline in September. The difference between observed and expected cases rose progressively during the summer from a slight negative value in June to a small positive difference in July, which increased in August and was greatest in September. After September, the differences were slight again, and on the negative side in October and November. In December and January, single cases occurred when the expectancy was nil or almost nil. Statistically, the monthly differences were not considered sig-

*Throughout the paper, differences are considered statistically significant if the values of probabilities are less than 0.05.

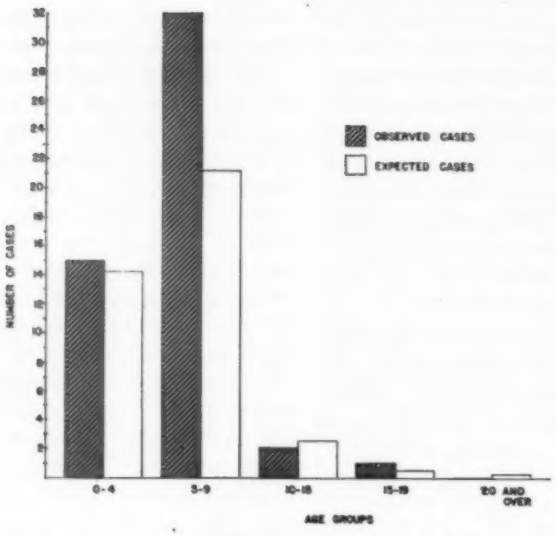

Chart 3.—Poliomyelitis following tonsillectomy in New York City hospitals in 1949 by age groups.

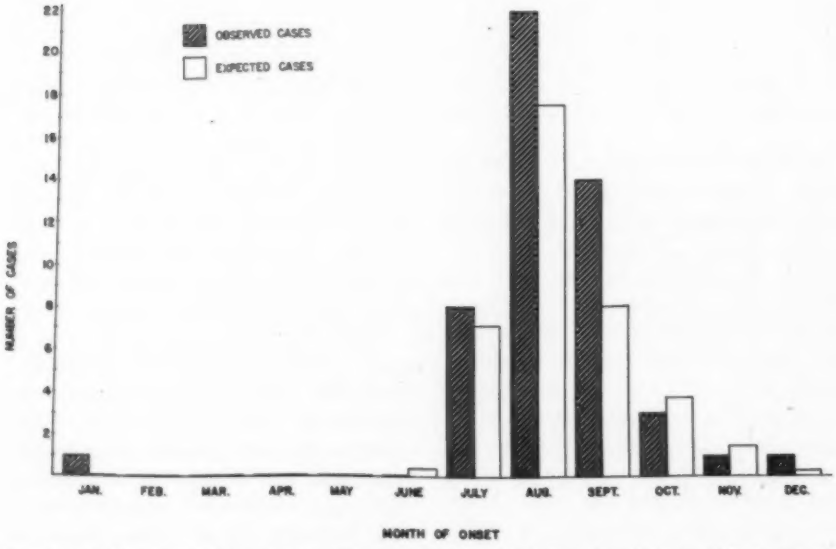

Chart 4.—Poliomyelitis following tonsillectomy in New York City hospitals in 1949 by month of onset.

nificant with the exception of the difference noted in September. The deviation of the actual from the expected pattern reflected a lag in the rate of decline of the epidemic in the tonsillectomized group or an increase in frequency in this group when the disease was most prevalent in the city.

The relationship of the month of operation to the occurrence of poliomyelitis is shown in Chart 5. The chart gives the number of cases observed and expected by month of operation regardless of date of onset of

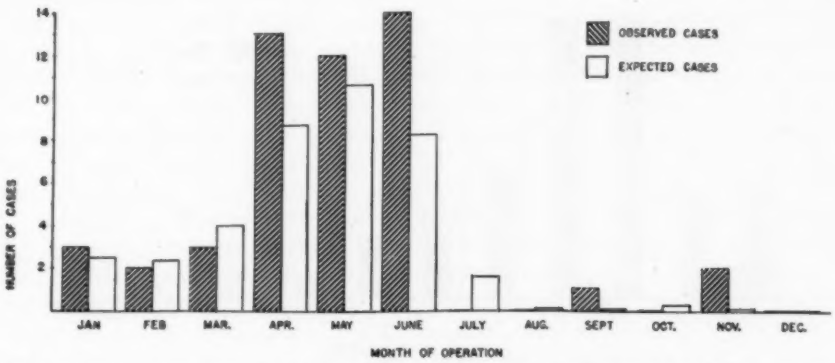

Chart 5.—Poliomyelitis following tonsillectomy in New York City hospitals in 1949 by month of operation.

poliomyelitis in 1949. The cases expected each month depended on the number of operations in a given month and the cumulative rate of incidence in the general population from the time of operation through December. To determine the cases expected by month of operation, the number of operations in each group during a given month was multipled by the total rate of incidence in the respective age group after the month plus half the rate during that month. The sum of the cases expected in each group gave the total expected for all age groups for a given month. For example, the cases expected for those tonsillectomized in July were equal to the number of operations in July by age group multiplied by the cumulative rate of incidence of the respective age groups from August through December plus half the rate in July.

The cumulative rate of incidence from a given calendar month through December was greatest before July, when few cases had occurred in the general population. After the onset of the epidemic in July, the cumulative incidence for the remainder of the year decreased sharply as many cases were reported and deducted from the total for the year. Consequently, those tonsillectomized before July experienced the full weight of the epidemic that followed, and the expected number of cases each month was highest, varying directly with the number of operations (Charts 1 and 5). For those tonsillectomized after July, the expected numbers were only small fractions of a case, either because the number of operations

were few, as in August, or because the cumulative incidence during the last months of the year was low.

The comparison of the observed and expected number of cases by month of operation revealed no consistent difference in the first three months of the year. In the second quarter of the year positive differences between observed and expected cases were statistically significant for the quarter. After June, the expected and observed number of cases were too small for the differences to be statistically significant. However, it is noteworthy that two cases developed shortly after operations performed in November, at the tail end of the outbreak, when the expectancy was 0.1 of a case out of 4,931 operations.

The consistently positive differences noted in April, May, and June indicated that operations in the spring might be hazardous, particularly in June, under the epidemic conditions prevailing in New York City during the succeeding months. The two cases observed in the November group of operations seemed to indicate that postponement of elective operations to the tail end of the outbreak was not necessarily a safeguard against poliomyelitis in all operations. The safest months for operation under the conditions prevailing in New York City in 1949 appeared to be the first three months and the last month of the year.

The relationship of the time interval between operation and onset of poliomyelitis is presented in Chart 6. The results are given by monthly intervals after operation regardless of month of operation or date of onset. In calculating the cases expected each month after operation, it was assumed that those subjected to operation in a given month were centered at the middle of that month. It was accordingly necessary to determine new monthly incidence rates consisting of the second half of one month and the first half of the succeeding month to measure the rates by monthly intervals after operation. Thus, for operations in January, the incidence rate during the first month after operation is the incidence in the latter half of January and the first half of February; for the second month after operation, the incidence

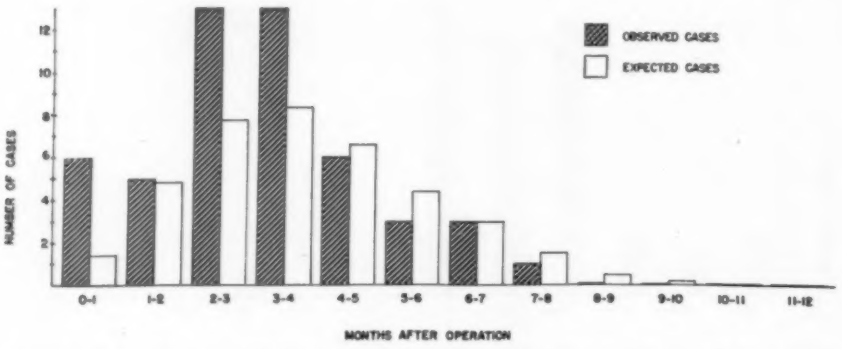

Chart 6.—Poliomyelitis following tonsillectomy in New York City hospitals in 1949 by monthly intervals after operation.

rate is the incidence during the latter half of February and the first half of March, etc. To determine the expected number of cases during the first month after operation, the number of operations in each calendar month was multiplied by the respective first month rates and the product summed. Similarily, the operations in each calendar month were multiplied by the second month rates to determine the expected number during the second month after operation, and so on for each month after operation.

The distribution of expected values by monthly intervals after operation followed an asymmetrical curve skewed to the right with the mode at 3 to 4 months after operation (Chart 6). The shape of the curve reflected the seasonal fluctuation in the number of operations and incidence of poliomyelitis shown in Charts 1 and 2, respectively. The concentration of expected cases between two and four months after operation was related to the large number of operations in April, May, and June from two to four months before the epidemic reached its peak. On the other hand, the expectancy of only 1.7 cases within the first month after tonsillectomy was related to the few operations performed during the height of the epidemic.

The observed cases followed the same general distribution noted among the expected cases with the exception of a secondary peak at 0 to 1 month. The significance of this positive deviation from the expected distribution pattern was enhanced by the fact that relatively few operations were done during the summer when the risk of infection within one month of operation was greatest. At 1 to 2 months there was almost no difference between the observed and expected number of cases, while at 2 to 3 and 3 to 4 months the positive differences were again relatively large and statistically significant when combined. After the fourth month the differences were small and tended to be on the negative side. On the whole, therefore, the evidence pointed to an increase in incidence during the first month following operation and possibly for as long as three to four months after tonsillectomy.

DISCUSSION

One of the purposes of the study was to develop a method for measuring the relationship of tonsillectomy to the incidence of poliomyelitis. The method employed was based on a comparison of reported cases and those expected on the assumption that there was no difference between tonsillectomized and nontonsillectomized groups. Corrections were made for age, time of operation, seasonal incidence of poliomyelitis, and duration of follow-up in 1949. By the method employed, such factors as month of onset, month of operation, and interval between operation and onset could be analyzed by age group.

The scope of the study was necessarily limited in time and place by the data available. Only the data on individuals tonsillectomized in New York City hospitals in 1949 were used, because their total population at risk was known. All others were excluded at the onset of the study because reliable and complete data on the number of operations performed outside of hospitals could not be obtained. Since the excluded cases were comparable to those in the study with regard to their

clinical types of poliomyelitis and other definable characteristics such as age, month of onset and of operation, it was assumed that their exclusion reduced the size of the sample without significantly altering its quality.

Despite the fact that there were 53,007 individuals in the tonsillectomized population under consideration, the number of cases of poliomyelitis in this group was small, because of the low incidence of poliomyelitis, and the relatively few operations during the summer. The differences between observed and expected cases were often not great enough to rule out sampling variation or were at the borderline of statistical significance. Consequently, additional data collected over a period of years will be needed for an accurate and detailed appraisal of the relation of tonsillectomy to the incidence of poliomyelitis at different intervals after operation. With the information available, only a preliminary report could be made on methods, the broader aspects of the problem, and suggestive inferences under the conditions prevailing.

Although the differences between observed and expected cases reported in the present study were not extreme, they indicated that tonsillectomy predisposed to clinical infection under certain circumstances. The most vulnerable group appeared to be the one with the highest attack rate. The hazards seemed to be greatest at the height of the epidemic, and were most evident shortly after operation, and among those tonsillectomized in the spring, particularly in June.

The relatively low number of operations performed during the height of the epidemic was a tribute to the hospitals and surgeons of New York City, who refused to operate when the risk of infection seemed greatest. The extent of the risk, for cases occurring within one month after operation, appeared to be several times greater among tonsillectomized individuals than among others of comparable age in the general population. It is therefore highly probable that our results, although statistically significant, would have been more impressive if more children had been subjected to tonsillectomies in July, August, and September, when virus of poliomyelitis was widely prevalent in the city and the likelihood of clinical infection within a month after operation increased. Contrariwise, many operations in the winter, when the risk of infection was nil, would have added to the total tonsillectomized a large group having no increase in incidence and thus would have reduced the over-all difference between tonsillectomized and nontonsillectomized individuals. Consequently, data weighted by many operations performed when the incidence is very low are unsatisfactory unless the risk of infection and the occurrence of poliomyelitis at varying periods following tonsillectomy are considered.

Unfortunately, there were no reliable criteria for forecasting the epidemic before its onset to have any effect on the large number of operations done in the spring. Furthermore, the postponement of operations until the tail end of the epidemic was not an absolute guarantee of safety, since poliomyelitis developed shortly after the removal of tonsils and adenoids in November when its occurrence seemed unlikely. In other

words, the poliomyelitis season was not limited to July, August, and September when the incidence was greatest, but was prolonged through October, November, and part of December. Consequently, the safest period for elective operations in New York City in 1949, from the point of view of risk of poliomyelitis, would seem to have been the months of January, February, and March.

SUMMARY

1. A method has been presented for measuring the relation of tonsillectomy to the incidence of poliomyelitis by age group, month of onset, month of operation, and time interval between operation and onset.

2. The study was limited to 53,007 operations performed in the hospitals of New York City in 1949 when the city experienced its third largest epidemic of poliomyelitis.

3. From data obtained in New York City during an epidemic year, it appears that tonsillectomy predisposes to the development of clinical symptoms of poliomyelitis.

We are grateful to Dr. John W. Fertig, Professor of Biostatistics at Columbia University, for reviewing the manuscript and the statistical methods used, and for his many helpful suggestions.

Dr. W. Lloyd Aycock of the Harvard School of Public Health offered constructive criticisms.

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TONSILLECTOMY AND POLIOMYELITIS

II. Frequency of Bulbar Paralysis, 1944-1949

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IN A PREVIOUS report, evidence of an increase in the incidence of poliomyelitis shortly after tonsillectomy was presented.[1] In the present study, the clinical types of poliomyelitis encountered in post-tonsillectomized cases were investigated.

The possible relationship of bulbar paralysis to tonsillectomy was noticed as far back as 1910.[2] In 1928 and 1929, two reports were made on the large percentage of post-tonsillectomized cases of poliomyelitis with bulbar paralysis.[3, 4] After 1929, there were numerous accounts of single or multiple cases of bulbar paralysis occurring shortly after tonsillectomy.[5-23] Since 1940, however, reports of surveys on the incidence of poliomyelitis in tonsillectomized populations, made chiefly by laryngologists, have stressed the infrequency of clinical infection following operation and by inference the rarity of bulbar paralysis in such cases.[1, refs. 1-13] Consequently, considerable confusion has arisen and doubt has been expressed over the relationship of bulbar poliomyelitis to recent tonsillectomy even though the association had seemed so well established on clinical[2-23] and experimental grounds.[24]

It therefore became necessary to reexamine the problem of bulbar paralysis following tonsillectomy. Two methods of approach were considered. One was based on an analysis of incidence of bulbar poliomyelitis in tonsillectomized and nontonsillectomized groups from data collected in 1949. It was clear at the onset of that study that poliomyelitis was too uncommon, even during an epidemic year, to accumulate sufficient data for reliable deductions on such specific incidence from a survey conducted in 1949 alone.

The second approach to the problem was based on an analysis of the percentage distribution of clinical types of poliomyelitis following tonsillectomy. This has been the conventional method in the absence of sufficient data on the size of the tonsillectomized population at risk, and was employed in the present study.

METHOD

The sources of data examined were the records of cases of poliomyelitis reported to the Health Department of the City of New York prior to 1950. A review of the record cards revealed that a query on recent tonsillectomy was carried on all cards in use since 1944. The present study was therefore limited to all cases reported from 1944 to 1949, inclusive. Records of cases reported before 1944 were considered incomplete with respect to in-

From the Bureau of Preventable Diseases, New York City Department of Health.

formation on tonsillectomy and were omitted from the study.

The six-year period from 1944 to 1949 began and ended with epidemics in 1944 and 1949. The intervening years, from 1945 to 1948 inclusive, were nonepidemic. The epidemic and nonepidemic years were treated separately in preliminary tabulations and then combined to determine the outcome in all reported cases.

From 1944 to 1949, inclusive, 6,524 cases of poliomyelitis and 392 deaths were reported in New York City (Table I).

TABLE I

	CASES		DEATHS	
YEARS	NO.	RATE PER 100,000	NO.	CASE FATALITY (%)
1944	1,890	24.6	102	5.4
1945	545	7.1	37	6.8
1946	716	9.2	38	5.3
1947	224	2.9	10	4.5
1948	703	8.7	26	3.7
1949	2,446	30.0	179	7.3
	6,524	13.8	392	6.0

The reported cases included paralytic and nonparalytic forms of the disease. For purposes of analysis, the paralytic forms were broken down into spinal and bulbar types. The former consisted of cases with paralysis of spinal nerves only; the latter of all other paralytic cases commonly classified as bulbar or bulbo-spinal. Cases without evidence of paralysis or muscle weakness were called nonparalytic.

The so-called abortive forms of poliomyelitis lacked the necessary diagnostic criteria to be considered definite clinical cases of poliomyelitis and were currently excluded from the files of reported cases along with many misdiagnosed cases. On the average, the excluded cases comprised about 20 per cent of the total tentatively reported each year as poliomyelitis.

The findings were obtained by trained diagnosticians who examined all patients either at home or in the hospital usually within twenty-four hours after the illness had been reported. In most cases, additional data on affected parts of the body were obtained during convalescence.

RESULTS

A summary of the clinical types of poliomyelitis found in reported cases by year of onset is given in Table II. The percentage distribution of the various clinical types differed somewhat by year of onset. The differences between epidemic and nonepidemic years were not considered statistically significant. The average percentage for the entire period and the highest

TABLE II. CLINICAL TYPES OF POLIOMYELITIS REPORTED IN NEW YORK CITY (1944-1949)

		BULBAR		SPINAL		NONPARALYTIC	
YEAR OF ONSET	TOTAL	CASES	%	CASES	%	CASES	%
1944*	1,890	274	14.5	892	47.2	724	38.3
1945†	545	91	16.7	249	45.7	205	37.6
1946†	716	144	20.1	324	45.2	248	34.7
1947†	224	24	10.7	91	40.6	109	48.7
1948†	703	101	14.4	332	47.2	270	38.4
1949*	2,446	392	16.0	1,109	45.3	945	38.7
Total	6,524	1,026	15.7	2,997	45.9	2,501	38.4
*Epidemic years	4,336	666	15.4	2,001	46.1	1,669	38.5
†Nonepidemic years	2,188	360	16.5	996	45.5	832	38.0

and lowest percentages in single years are listed in Table III.

TABLE III

TYPE OF DISEASE	PERCENTAGES		
	AVERAGE	HIGH	LOW
Bulbar	15.7	20.1	10.7
Spinal	45.9	47.2	40.6
Nonparalytic	38.4	48.7	34.7

The types of paralysis also varied with the age group as shown in Table IV. The percentage of bulbar cases was lowest in the youngest age group. It varied from 10.6 per cent at 0 to 4 years to 18.8 per cent at 10 years and over, with an average of 15.7 for the six-year period.

group at any time was 30.1 per cent in 1945 for patients 20 years and over.

Among the reported cases described above, a history of tonsillectomy within one year of the onset of poliomyelitis was noted in 194 cases. These formed the basis of the present study.

Their distribution by monthly intervals between operation and onset in each year of occurrence is given in Table V.

The number of post-tonsillectomized cases each year was related in part to the total number reported, being largest for the epidemic years of 1944 and 1949 and smallest in nonepidemic

TABLE IV. CLINICAL TYPES OF POLIOMYELITIS REPORTED FROM 1944 TO 1949 BY AGE GROUP

AGE	TOTAL	BULBAR		SPINAL		NONPARALYTIC	
		CASE	%	CASE	%	CASE	%
0- 4	1,700	180	10.6	1,035	60.9	485	28.5
5- 9	2,209	355	16.1	859	38.9	995	45.0
10-14	1,373	258	18.8	510	37.1	605	44.1
15-19	572	107	18.7	271	47.4	194	33.9
20 and over	670	126	18.8	322	48.1	222	33.1
Total	6,524	1,026	15.7	2,997	45.9	2,501	38.4

TABLE V

YEAR OF ONSET	TOTAL	MONTHLY INTERVAL BETWEEN OPERATION AND ONSET OF POLIOMYELITIS				
		0-1	1-2	2-3	3-6	6-12
1944	59	10	13	7	22	7
1945	15	3	3	2	5	2
1946	20	4	5	2	8	1
1947	2	1	0	0	0	1
1948	24	6	4	2	9	3
1949	74	6	7	21	35	5
Total	194	30	32	34	79	19
Percentage	100	15.5	16.5	17.5	40.7	9.8

From the foregoing description of reported cases, it was seen that the percentage of bulbar, spinal, and nonparalytic cases observed from 1944 through 1949 differed somewhat by year of onset and age group. The frequency of bulbar paralysis tended to be lower among those under 10 years of age than in older groups. The maximum percentage in any age

years, particularly in 1947 when the incidence in the city was lowest. In each year, one or more cases occurred within a month after operation, the total for the six-year period being thirty cases or 15.5 per cent. Almost half of the cases had their onsets within three months of operation and 90.2 per cent within six months. In only 9.8 per cent was the interval between

operation and onset more than six months.

There were twelve deaths among the post-tonsillectomized cases of poliomyelitis, all within six months after operation. The distribution of deaths by monthly interval between operation and onset is shown in Table VI.

TABLE VI

INTERVAL BETWEEN OPERATION AND ONSET (MONTHS)	CASES	DEATHS	CASE FATALITY (%)
0-1	30	4	13.3
1-2	32	4	12.5
2-3	34	0	0.0
3-6	79	4	5.1
6-12	19	0	0.0
Total	194	12	6.0

The case fatality was 12.9 per cent in cases occurring within the first two months after operation and 3.1 per cent in cases occurring more than two months after. The difference was statistically significant.

The case fatality expected among the 194 cases on the basis of deaths by age group and by year of onset for all of the 6,524 reported cases was 4.4 per cent. It was significantly lower than the rate observed for cases occurring within two months after operation, and was indicative of a more severe form of poliomyelitis in cases occurring shortly after operation than in other groups of cases of comparable age and year of occurrence.

The deaths in the post-tonsillectomized cases occurred from one to eight days after the onset of symptoms of poliomyelitis. All of those who died had bulbar paralysis. The case fatality of bulbar poliomyelitis following tonsillectomy is given in Table VII by interval between operation and onset. The fatality of bulbar cases occurring within the first two months after operation was 30.8 per cent as against 18.2 per cent after the second month. The difference was not considered statistically significant for the small numbers in the groups.

TABLE VII

INTERVAL BETWEEN OPERATION AND ONSET (MONTHS)	BULBAR CASES	DEATHS	CASE FATALITY (%)
0-2	26	8	30.8
2-12	22	4	18.2

It was apparent that a study of the type of paralysis in 194 cases by various categories for the purpose of finding significant relationships would entail the analysis of small samples that could be misleading. In order to reduce the chances of error, the method of study based on the findings in all cases of poliomyelitis was supplemented by another method designed to reduce the element of bias and to facilitate comparisons between samples if the data on all cases were unknown. The method employed was based on the random selection of cases without a history of tonsillectomy which matched the post-tonsillectomized cases with respect to such known characteristics as age, sex, color, date of onset, and borough of residence. The randomly selected cases were called the "control group" or "matched sample."

The following procedure was followed in the selection of the matched sample. The post-tonsillectomized cases reported each year were removed from the files and charted by borough of residence and date of onset and assigned a case number in consecutive order starting with the earliest re-

ported case. All other cases reported in a given year, filed alphabetically by borough of residence, were reviewed in consecutive order. The first to match a postoperative case by age, sex, color, and date of onset was selected for the matched sample and given the case number of its counterpart in the postoperative group. Some leeway had to be allowed for cases that could not be matched exactly. In these instances, those chosen were closest to the date of onset and of the same sex, color, and age. In a few exceptions, either the sex differed, or the age differed by plus or minus one year within the same age group. By this process it was possible to select at random 194 reported cases of poliomyelitis without a history of tonsillectomy each of which was similar to a tonsillectomized case with respect to the characteristics noted above, and then to set the cases of one group against the matched cases of the other in studying the effects of tonsillectomy on poliomyelitis occurring after the operation.

The tonsillectomized cases and the matched sample were grouped by monthly interval between operation and onset. The results obtained are summarized in Table VIII giving the percentage of bulbar, spinal, and nonparalytic cases in each of the groups. The percentage of cases with bulbar paralysis varied from 56.7 per cent at 0 to 1 month after operation to 0 per cent at 6 to 12 months after operation. The percentage of cases with bulbar paralysis within one month of operation was two or more times greater than in any other group shown in the table, and almost twenty times greater than its comparable control group in the matched sample. After the first month, the differences in the percentage of bulbar paralysis between tonsillectomized and control groups were either nil or not statistically significant (Table VIII).

TABLE VIII. PERCENTAGE DISTRIBUTION OF CLINICAL TYPES OF POLIOMYELITIS BY MONTHLY INTERVAL BETWEEN OPERATION AND ONSET IN TONSILLECTOMIZED GROUPS, AND IN RANDOMLY SELECTED CONTROL GROUPS WITHOUT HISTORY OF TONSILLECTOMY

	MONTHLY INTERVAL BETWEEN OPERATION AND ONSET					
	0-1	1-2	2-3	3-4	4-6	6-12
	Tonsillectomized Groups					
Cases	30	32	34	46	33	19
Bulbar	56.7	28.1	20.6	17.4	21.2	0
Spinal	30.0	43.8	26.5	54.3	48.5	47.4
Nonparalytic	13.3	28.1	52.9	28.3	30.3	52.6
	Randomly Selected Control Samples					
Cases	30	32	34	46	33	19
Bulbar	3.3	25.0	20.6	17.4	6.1	5.2
Spinal	70.0	40.6	58.8	52.2	51.5	63.2
Nonparalytic	26.7	34.4	20.6	30.4	42.4	31.6

These results are shown graphically in Chart 1 which also gives the percentage of cases with bulbar paralysis expected on the basis of its frequency by age group and year of onset for the 6,524 cases reported from 1944 to 1949. The expected percentage of bulbar cases was 14.3 per cent. This was significantly different from the observed value of 56.7 per cent at 0 to 1 month. It was also consistently lower than the percentages observed up to 6 months after operation. Com-

pared with the matched samples, the expected value was lower in three groups and higher in three groups in keeping with the degree of sampling variation anticipated in randomly selected groups.

It was apparent from the studies that bulbar paralysis was more common than expected in cases of poliomyelitis occurring within one month after operation. After the first month of operation up to the sixth month, the results were inconclusive. At 6 to 12 months after operation, there were no indications of a predisposition to bulbar paralysis in the small group studied.

Since the results within one month of operation were statistically significant, they were treated separately in the description of the post-tonsillectomy cases which follows. The data from 6 to 12 months were omitted because there were no indications of any predisposition to bulbar paralysis during this period.

The clinical types of poliomyelitis observed among the post-tonsillectomized cases in epidemic and nonepidemic periods are given in Table IX.

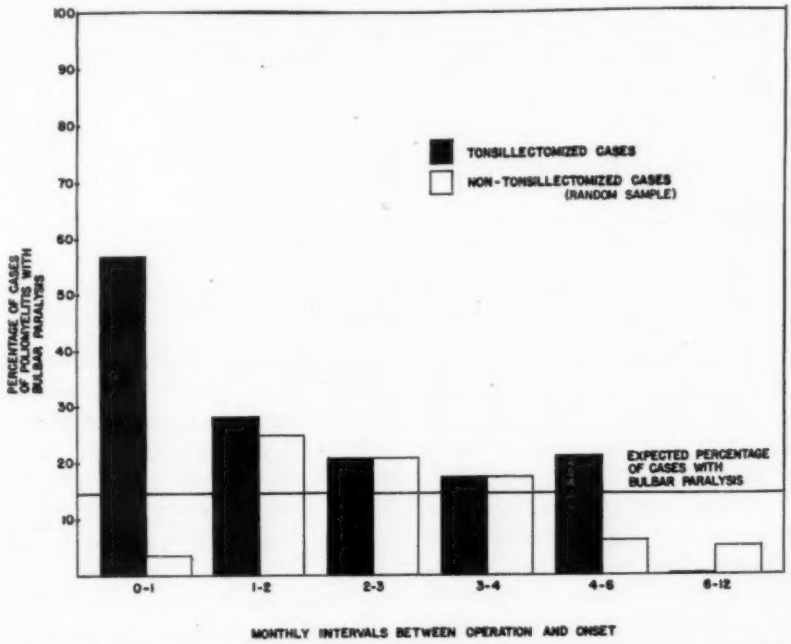

Chart 1.—Bulbar poliomyelitis by monthly intervals between operation and onset, New York City, 1944 to 1949.

Although the numbers were small, the predisposition to bulbar paralysis within a month after operation seemed to be more clearly evident during the nonepidemic years of 1945 to 1948 than in the epidemic years of 1944 and 1949. Eleven of the seventeen bulbar cases observed in the first month occurred in nonepidemic years. During these years, the percentage of

TABLE IX

YEAR	0-1 MONTH BETWEEN OPERATION AND ONSET				1-6 MONTHS BETWEEN OPERATION AND ONSET			
	TOTAL	BULBAR	SPINAL	NONPARALYTIC	TOTAL	BULBAR	SPINAL	NONPARALYTIC
1944	10	4	4	2	42	8	23	11
1945-48	14	11	2	1	40	10	16	14
1949	6	2	3	1	63	13	34	16
Total	30	17	9	4	145	31	73	41

TABLE X

MONTH OF ONSET	0-1 MONTH BETWEEN OPERATION AND ONSET				1-6 MONTHS BETWEEN OPERATION AND ONSET			
	TOTAL	BULBAR	SPINAL	NONPARALYTIC	TOTAL	BULBAR	SPINAL	NONPARALYTIC
January	1	0	1	0	0			
February	0				0			
March	0				0			
April	0				0			
May	1	1	0	0	0			
June	1	1	0	0	1	1	0	0
July	5	2	2	1	24	7	12	5
August	7	4	2	1	63	15	30	18
September	5	2	2	1	40	5	24	11
October	5	5	0	0	10	3	3	4
November	3	1	2	0	3	0	1	2
December	2	1	0	1	4	0	3	1
Total	30	17	9	4	145	31	73	41

patients with bulbar paralysis within the first month of operation was about twice that observed in the epidemic years. At 1 to 6 months after operation, the frequency of bulbar paralysis in epidemic and nonepidemic years was 20 per cent and 25 per cent, respectively. The high frequency of bulbar paralysis during nonepidemic years indicates that the hazards of tonsillectomy were not limited to epidemic periods.

The relationship of post-tonsillectomized cases to month of onset is shown in Table X. The distribution of cases from 1 to 6 months after operation paralleled the seasonal incidence of the disease with about 80 per cent in the summer and 20 per cent in the fall.* However, cases occurring within a month of operation showed less dependence on seasonal incidence and a more even distribution so that 57 per cent occurred in the summer, 33 per cent in the fall, and 10 per cent in the winter and spring.

Where cases of poliomyelitis occurred within the first month after operation, the percentage of patients with bulbar paralysis was almost always high regardless of month of onset. The percentages were somewhat higher in the spring and fall than in the summer. However, no bulbar cases were observed during the winter. It therefore seems that timing the operation in the spring and fall was in itself no safeguard against the development of bulbar paralysis, and that the winter is the least dangerous for elective operations from the standpoint of poliomyelitis.

*The terms winter, spring, summer, and fall refer to the first, second, third, and fourth quarters of the year.

TABLE XI

AGE	0-1 MONTH BETWEEN OPERATION AND ONSET				1-6 MONTHS BETWEEN OPERATION AND ONSET			
	TOTAL	BULBAR	SPINAL	NONPARALYTIC	TOTAL	BULBAR	SPINAL	NONPARALYTIC
0- 4	11	9	2	0	68	13	38	17
5- 9	14	6	6	2	69	17	31	21
10-14	4	2	0	2	5	0	3	2
15-19	0	0	0	0	2	0	1	1
20 and over	1	0	1	0	1	1	0	0
Total	30	17	9	4	145	31	73	41

TABLE XII

SEX	0-1 MONTH BETWEEN OPERATION AND ONSET				1-6 MONTHS BETWEEN OPERATION AND ONSET			
	TOTAL	BULBAR	SPINAL	NONPARALYTIC	TOTAL	BULBAR	SPINAL	NONPARALYTIC
Male	19	11	6	2	81	16	32	33
Female	11	6	3	2	64	15	41	8
Total	30	17	9	4	145	31	73	41

TABLE XIII. CLINICAL TYPES OF POLIOMYELITIS FOLLOWING TONSILLECTOMY BY INTERVALS OF DAYS AND WEEKS BETWEEN OPERATION AND ONSET FOR CASES OCCURRING WITHIN THE INCUBATION PERIOD

	INTERVAL IN DAYS AND WEEKS BETWEEN OPERATION AND ONSET									
	FIRST WEEK		SECOND WEEK		THIRD WEEK		FOURTH WEEK		FIFTH WEEK	
	DAYS	CASES*	DAYS	CASES	DAYS	CASES	DAYS	CASES	DAYS	CASES
	1	S	8	B	15	B,B	22	B,S	29	--
	2	--	9	B,B,B	16	N	23	--	30	B
	3	B	10	--	17	B	24	--	31	N
	4	--	11	B,S	18	B,S	25	S	32	S
	5	--	12	B,S	19	B	26	N	33	--
	6	B	13	--	20	--	27	--	34	--
	7	B	14	B,B	21	B,S,N	28	N	35	--
Totals		4		10		10		5		3
Bulbar		3		8		6		1		1
Spinal		1		2		2		2		1
Nonparalytic		0		0		2		2		1

*The letters designate the clinical form in each case, viz., B = Bulbar, S = Spinal, N = Nonparalytic, -- = No case.

The cases of bulbar paralysis in various age groups is shown in Table XI. As expected, most of the bulbar cases were under 10 years of age because the number of the operations and incidence were greatest in this age group. The frequency of bulbar paralysis was high within a month after operation in all age groups in which more than one case occurred, and somewhat higher under 5 years of age than 5 years and over. Excluding the age groups 15 years and over, for which there were insufficient data, the predisposition of post-tonsillectomized cases to bulbar paralysis did not seem to be dependent on age.

The numbers were too small for analysis by sex and age combined, so that the distribution of type of paralysis by sex alone is given in Table XII. Males predominated in a ratio of 57:43 which was comparable to the sex ratio observed for all cases. The

differences in the percentage of bulbar cases among males and females were not significant.

The relationship of the clinical types of poliomyelitis occurring shortly after operation to the incubation period of the disease is shown in Table XIII by intervals of days and weeks between operation and onset. All cases occurring within thirty-five days after operation, the extreme upper limit of the incubation period, are presented in Table XIII. The cases were widely scattered during the presumed incubation period of the disease, most of them occurring in the second and third weeks after operation. The frequency of bulbar paralysis decreased progressively from 78 per cent in the first two weeks after operation, to 60 per cent in the third week, and to 25 per cent after that. The period with the highest percentage of bulbar cases was less than twenty-one days between operation and onset, which corresponded to the usual incubation period.

DISCUSSION

The data obtained in New York City in recent years confirm the results reported from other sources on the predisposition of recently tonsillectomized cases of poliomyelitis to bulbar paralysis.[2-23] The relationship between bulbar paralysis and tonsillectomy seems firmly established for cases occurring within one month of operation. It was most marked in the first three weeks or within the usual incubation period of poliomyelitis. The duration of the predisposition to bulbar poliomyelitis could not be precisely ascertained from the available data. There was some indication of its persistence for as long as six months in certain cases, but the results on the frequency of bulbar paralysis after the first month were not statistically significant, nor demonstrable by all methods of analysis.

The increased frequency of bulbar paralysis after operation was accompanied by an increase in case fatality. The increase in case fatality was greater than expected for cases of poliomyelitis occurring within the first two months after tonsillectomy. It represents additional evidence that the danger period after tonsillectomy may last for more than one month in some cases.

The predisposition to bulbar paralysis observed within one month after operation was more evident in non-epidemic years than in epidemic years, and in the spring and fall, than in the summer. The influence of these two time factors could not be accurately measured, because the number of cases was too small for the extent of the differences observed. Both were related to periods when the incidence of poliomyelitis was not maximal and when the number of operations was presumably increased. Regardless of the explanation, the high frequency of bulbar paralysis when the incidence of poliomyelitis was not inordinately high represented a hazard that might be considered in scheduling elective operations.

In this connection, it is significant that no cases of bulbar paralysis following tonsillectomy were encountered during the winter months. The absence of bulbar cases in the winter was associated with the infrequency of all forms of poliomyelitis during this

period, and added weight to the impression gained from studies on incidence that the winter months are the safest for tonsillectomy.[1] With modern chemotherapy, it might be feasible either to reduce the number of tonsillectomies or to schedule more operations for the winter and fewer for other seasons. The shift in timing would not only conform to the current trend of postponing elective operations during the poliomyelitis season, but would also take into consideration the possibility of an oncoming epidemic.

One of the difficulties in the study was the necessity of working with small samples because of the low incidence of poliomyelitis. In order to check the results and reduce the element of bias, comparative tests were made against randomly selected cases without a history of tonsillectomy and similar to the tonsillectomized in such known characteristics as age, sex, borough of residence, and date of onset. The method was applicable to the study of such factors as type of paralysis and course, and is useful when data on all reported cases are not available.

The results obtained in the present report on bulbar paralysis supplemented those in the previous report on incidence of poliomyelitis. While the available data on incidence revealed no increase in the number of patients observed at 0 to 4 years of age, a well-marked predisposition to bulbar paralysis was noted in this age group within one month after operation. At 5 to 9 years of age, the combined evidence pointed not only to a greater percentage of bulbar cases but also to a greater number of cases.

SUMMARY

1. A study was made of the frequency of bulbar paralysis in 194 cases of poliomyelitis occurring within one year of tonsillectomy. Those in the study were selected from a total of 6,524 cases of poliomyelitis reported in New York City from 1944 through 1949.

2. Two methods of analysis were employed, one based on the corrected expectancy of bulbar paralysis from its distribution among all cases reported during the six-year period under consideration, the other based on the results in a randomly selected group of cases without a history of tonsillectomy and comparable to those tonsillectomized with respect to age, sex, borough of residence, and date of onset.

3. By both methods employed in the study, the percentage of bulbar paralysis was significantly higher than expected among post-tonsillectomized cases within one month of operation. The results were inclusive from one to six months after operation. No increase in the percentage of bulbar paralysis could be demonstrated in a small group of cases from six to twelve months after operation. The critical period when bulbar paralysis was most common was the first three weeks following operation.

4. An increase in case fatality was noted among cases occurring within two months after operation.

CONCLUSION

The data presented support the view that cases of poliomyelitis occurring shortly after tonsillectomy are predisposed to bulbar paralysis.

Under the conditions prevailing in New York City from 1944 to 1949 with respect to poliomyelitis, the most desirable months for elective operations seem to be the winter months which are farthest removed from the poliomyelitis season.

We are grateful to Dr. John W. Fertig, Professor of Biostatistics at Columbia University, for reviewing the manuscript and the statistical methods used, and for his many helpful suggestions.

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JUVENILE TYPE OF WERNER'S SYNDROME

Progressive Musculocutaneous Dystrophy Observed for Eighteen Years

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THE subject of this case report, whose present appearance is shown in Fig. 1, has been observed by one of us (J. V.) since birth on March 15, 1932. This unusual, progressive, and crippling disorder has defied satisfactory diagnostic classification, and therapy has necessarily been limited to supportive and symptomatic measures. Survival for nearly two decades is remarkable.

CASE REPORT

At the age of 18 years, W. O. was admitted to the Los Angeles Children's Hospital for correction of a moderate degree of anemia and for diagnostic study. His complaints on entry were anorexia and pain in the muscles and joints, especially those of the lower extremities. Occasional small amounts of fresh blood had been noted in the stool. The photographs of the patient and the roentgenograms (Figs. 1-8) are more instructive than pages of description.

The patient was a pathetic, deformed, and underdeveloped male, who weighed 51½ pounds and whose rump-crown length (sitting height) was 28½ inches. He was immobilized in the sitting position by rigidity in flexion of the elbow and knee joints, although a fair degree of motion was permitted at the shoulders and hips. On the forearms and legs, subcutaneous tissue was absent, the overlying skin being atrophic, firm, and tightly drawn. Areas of telangiectasis were numerous. All underlying structures in the extremities were firm, bound-down, rigid, and apparently fused into a mass of almost cartilaginous consistency. The hands and feet were waxen in appearance with extreme atrophy of the digits. The skin was tightly stretched like a drumhead over the palms and soles, and numerous small areas of ulceration and hyperkeratosis were present on both heels. All of the nails were dystrophic and deformed, some being replaced by green crusts.

The skin and subcutaneous structures of the trunk and neck were less involved, although they felt thickened and doughy. The facies (Fig. 2) was remarkable because of saddlenose. The thin skin over the face, nose, mouth, and ears was stretched tight, giving a drawn appearance. There was abundant scalp hair and a sparse, fuzzy beard. The conjunctival, scleral, corneal, and mucosal surfaces and the teeth were normal.

The genitalia, which were otherwise normal, were developed to approximately the level of early puberty. Pubic hair was sparse and noncurly.

Emotional and mental development was retarded to the 11-year level, having been greatly influenced by chronic invalidism.

In all areas where the skin was involved, there were scattered firm nodules of irregular shape, some of which were erythematous. They ranged in size from a few millimeters to one or two centimeters in diameter.

The physical examination otherwise revealed a soft systolic heart murmur, heard over a limited area at the left sternal border. The heart was not enlarged and compensation was good. Blood pressure in the arm was 126/80.

From the Department of Pediatrics of the University of Southern California School of Medicine and the Children's Hospital, Los Angeles.

Fig. 1.—"Fixed-sitting" position of our patient after eighteen years of progressive deformity.

Fig. 2.—Profile of our patient shows the normal growth of hair, the saddle deformity of nose, the tightly drawn skin about the mouth and the bridge of the nose, and thinning of the helix of the ear.

The lungs were normal. The firm spleen was palpable 4 cm. below the costal margin. The liver was not enlarged. The proctoscopic examination showed no abnormality. The neurological examination was within normal limits, and all the special senses were intact.

Radiographic Examination.—Radiograms of the extremities (Figs. 5-8) showed marked gross deformity of the hands and feet, with extensive bony demineralization and osteoporosis. The fascial planes of the legs and forearms were widely calcified. The knee and elbow joints were narrowed and

Fig. 3.—Note the ankylosis of elbows, the taut skin, the loss of subcutaneous tissue in the forearms, and the deformity of the hands. The waxy infiltrated pad of the palms is suggested in the view of the left hand.

Fig. 4.—Close-up of the patient's feet. A biopsy of one of the nodules of the leg was done. Note the hyperkeratosis and areas of necrosis of the toes, and the waxlike infiltration and deformity of the feet.

Fig. 5.

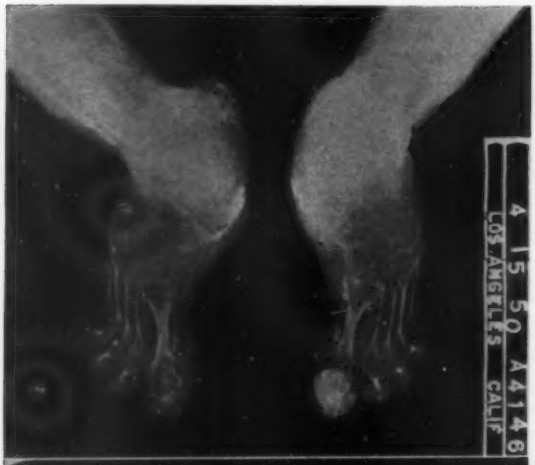

Fig. 6.

Fig. 5.—Roentgenogram of the feet, showing absorption of bone in the spindlelike metatarsals and deposits of calcium in the fascial planes.

Fig. 6.—Lateral roentgenogram of the femur, the tibia, and the fibula. Note the marked osteoporosis and the deposits of calcium in the fascial planes of the leg and foot.

largely obliterated by the ankylosis. The shoulder and hip joints were normal, as were the lung fields, the cardiac silhouette, and the cranial vault. No abnormality in the upper gastrointestinal series or in the barium enema could be demonstrated.

Laboratory.—The routine hematologic study showed no abnormality except moderate hypochromic normocytic anemia, hemoglobin 6.7 Gm. (43 per cent), which was corrected to normal value by repeated blood transfusions during the hospital stay. The urine was normal, and the complement fixation test for syphilis gave negative results. The blood sedimentation test (Westergren) was 106 mm. in one

Fig. 7.

Fig. 8.

Fig. 7.—Lateral roentgenogram of the ankle and the foot.

Fig. 8.—Roentgenogram of the patient's hands, showing osteoporosis and deformities of the metacarpals and phalanges. Note the calcium deposits in the fascial planes of the forearms.

hour. The blood contained, per 100 c.c., 7.6 mg. calcium, 4.6 mg. phosphorus, 4.0 mg. uric acid, and 5.2 Bodansky units of alkaline phosphatase. The Sulkowitch test of the urine showed slightly decreased calcium excretion. No uric acid crystals were noted in scrapings from the hyperkeratotic areas of the fingers and toes.

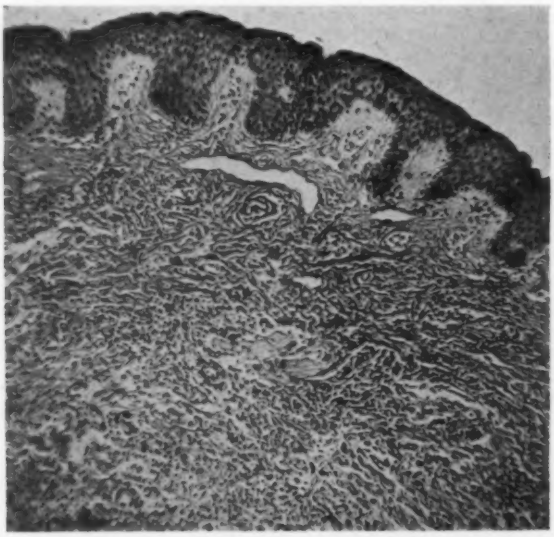

Fig. 9.—Low-power magnification of the skin, showing diffuse involvement.

Biopsy Study of Skin (Figs. 9, 10, and 11).—There was considerable hyperkeratotic debris on the surface. The epithelium was of normal thickness, and its rete pegs were of normal depth, although some appeared to be wider than usual. Some areas of the corium appeared normal; others exhibited marked focal changes. In the latter areas, there was a diffuse infiltration of cells, chiefly lymphocytes with occasional eosinophiles, throughout the corium. The reaction extended to the subcutaneous fat in some areas. This cellular infiltrate was sometimes related to arterioles, but was usually independent of such association. Polymorphonuclears were occasionally present, and one section showed an acute inflammatory reaction in the corium with marked deeper infiltration of polymorphonuclear leucocytes into the subcutaneous fat. There were foci of necrosis of the collagenous components of the corium, particularly in some areas where the cellular infiltration was most prominent. The connective tissue generally appeared distinctly hyaline, and its fibers broad and intensely stained. Occasionally small circumscribed areas of calcification were noted; these were not accompanied by inflammatory reaction. A section of striated muscle was not remarkable.

Family History.—Both parents are living and well, and no similar or related disorder has occurred in the antecedents of the patient or in collateral branches of the family. The patient's mother had three spontaneous abortions in the first trimester of all other pregnancies; there are no siblings. Syphilis in either parent has been excluded by thorough and repeated study.

Past History.—Pregnancy was uneventful. The delivery was normal at term; birth weight was 6 pounds, 7 ounces. When 1 week old, the infant developed a bizarre eruption on the skin of the trunk and extremities, the persistence of which led to further consultation and diagnostic study at the Los Angeles Children's Hospital in August, 1932. At this time, the skin of the 5-month-old infant exhibited numerous discrete, slightly elevated, firm maculopapules of irregular size and shape, averaging a few millimeters in diameter and scattered over the trunk and extremities. The hemoglobin was 36 per cent (Sahli). He preferred to remain in one position and cried when his extremities were moved; pressure on long bones evoked tenderness. The spleen was easily felt. There was a saddlenose. Roentgen-

Fig. 10.

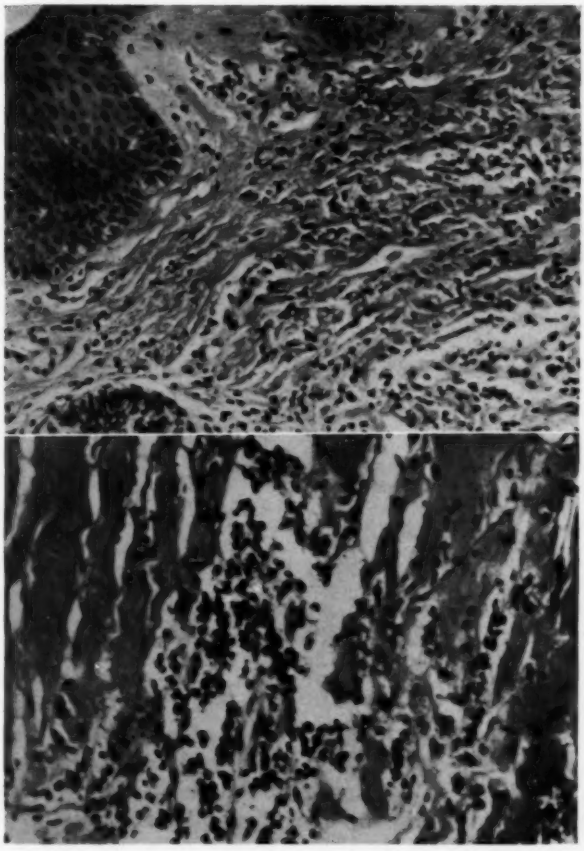

Fig. 11.

Fig. 10.—Intermediate power of the skin, showing cellular infiltrate and collagenous changes.

Fig. 11.—High-power magnification of the corium, showing chronic inflammatory reaction and collagenous necrosis.

ograms revealed the long bones were then normal, and repeated provocative blood Wassermann tests remained negative. No diagnosis was established at that time.

Two months later, biopsy of an enlarged inguinal lymph node failed to explain the persistent signs and symptoms. At 1 year of age, insufficient uninvolved skin remained to permit performance of skin sensitization tests.

When 16 months old, the patient was studied at a Chicago hospital.[1] The previously described disorder had become complicated by daily fevers with temperature ranging as high as 104° F. Painful contractures and swellings were developing in the knees, elbows, and phalanges. Aluminum splints were applied, and the possibility of Still's disease was considered.

At 2 years of age, the patient was a small, irritable child with persistent skin rash, painful and swollen joints, and almost daily fever. He could stand, and he walked with help. Despite conventional orthopedic care, his deformity and disability progressed slowly. At 4 years of age, tricycle riding was discontinued because of inability to grip the handle bar.

When 5 years old, he was admitted to a hospital in Chicago.[2] Because of skin lesions, muscle tenderness, rigid extremities, hypochromic anemia, splenomegaly, increased blood sedimentation rate, abnormal creatinuria, and muscle and skin biopsy, a diagnosis of poikilodermatomyositis was considered established.

In the subsequent years, disability has relentlessly progressed to the degree described in this report. In 1938, 1939, and 1943, he survived attacks of bronchopneumonia. Orthopedic treatment has been abandoned, and at present his care is symptomatic, expectant, and custodial. He requires large amounts of analgesics, and leads a fairly comfortable bed-and-chair existence.

At the time of publication, the patient is receiving cortisone in conventional adult dosage.

There has been remarkable improvement in appetite, weight gain, and in sense of well-being; there has been no significant change in the appearance of his skin, and his disability remains as profound as ever.

DISCUSSION

Dermatomyositis, as described by Steiner,[3] may have a gradual onset with vague and indefinite prodromas, followed by edema, dermatitis, and multiple muscle inflammation. The acute stage may last about two months, and death usually follows. The subacute stage may last six to twelve months, and the chronic, from two to three years, with recovery in about 50 per cent of the cases. Contractures of joints and deposits of calcium in subcutaneous tissue may occur. In dermatomyositis, contractures and ankylosis of the joints usually occur in the proximal joints, whereas in our case, the proximal joints (shoulders and hips) were the least involved. O'Leary and Waisman[4] say that the most difficult to distinguish from dermatomyositis in the early stages are diffuse scleroderma in its edematous stage and scleredema adultorum (Buschke). The latter appears in the wake of some acute infectious disease. Beginning with brawny swelling on the neck, it spreads upward over the face and downward over the arms and trunks in a few weeks. They also state that trichinosis must be ruled out by muscle biopsy in each case of suspected dermatomyositis, because the symptomatology may be identical in the two diseases. In our case, no trichinae were found in sections from the deltoid muscle.

Scleroderma is a disease affecting the collagenous connective tissue of

the skin in circumscribed patches (morphea), or in the diffuse form, which soon transforms the patient into a waxen image. An acute infection or a period of fever, anorexia, weight loss may occasionally precede the onset of the diffuse or generalized scleroderma, and may confuse it with scleredema adultorum. In the early stage, there are edema and induration; later, atrophy of the skin, muscle, fascia, and bone develops; any organ may be involved. The skin assumes a smooth, waxy, tightly stretched look, and may have an ivory-yellow or dirty brown pigmentation. When the hands and feet become involved, contractures develop, and the underlying bones show a marked osteoporosis; calcium deposits in the subcutaneous tissues and muscles may also be seen. The etiology of scleroderma is obscure, but a nonspecific capillary endarteritis has been suggested as the cause.

Diffuse scleroderma is rare in the first twenty years of life; most patients die two to five years after the onset. Involvement of the esophagus (dysphagia) and colon may be demonstrated by roentgenologic examination, using barium contrast media to demonstrate the lack of peristaltic waves; this gives a tubelike appearance to the involved portions of the gastrointestinal tract. Our patient showed no such involvement of his esophagus or colon.

Diffuse scleroderma usually involves the face and scalp, giving the patient the appearance of a newly hatched chicken. Our patient had thin, shiny skin over the ears, bridge of nose, and about the mouth, but the scalp and hair and eyebrows were normal in amount and color. The blood is usually normal, phosphatase normal, excretion of calcium diminished, and creatinuria found in most cases.

Fig. 12.—A 12-year-old boy reported by Pachman as a case of scleroderma. This patient died one and one-half years later.

The biopsy lesions in our patient were taken from the (a) nodular areas on the tibia, (b) scleroderma-like patch with telangiectatic areas of the overlying tight skin, and (c) nodular skin in the suprascapular area. The

TABLE I. WERNER'S SYNDROME (PROGERIA OF THE ADULT) AND ROTHMUND'S SYNDROME: TWO TYPES OF CLOSELY RELATED HEREDOFAMILIAL ATROPHIC DERMATOSES WITH JUVENILE CATARACTS AND ENDOCRINE FEATURES; A CRITICAL STUDY WITH FIVE NEW CASES[11]

SYMPTOMS	WERNER'S SYNDROME	ROTHMUND'S SYNDROME	CATARACTA DERMATO-GENES WITH NEURO-DERMITIS	PROGERIA OF CHILDREN WITH NANISM	MYOTONIC DYSTROPHY	ECTO-DERMAL DYS-PLASIA WITH DYS-TROPHY OF HAIR AND NAILS
Heredofamilial occurrence	+++	+++	±	0	++	+++
Age at the beginning of disorder	20-30 yr.	3 mo.-3 yr.	3-20 yr.	2-5 mo.	20-30 yr.	Shortly after birth
Shortness of stature	+++	+	0	++++	+	0
Skin changes	++++	++++	++++	+	+	++
(a) Tightly drawn over underling tissue	++++ 20-30 yr.	0	0 3-20 yr.	+ 2-5 mo.	+ 20-30 yr.	0 Shortly after birth
(b) Atrophic and thin skin	++++	++	++	++	++	+
(c) Telangiectases	+	++++ 3 mo.	0	0	0	0
(d) Scaling	++	++++	++++	+	0	0
(e) Pigmentation and depigmentation	+	+++	++	+	+	0
(f) Ulcers	++++	0	0	0	+	0
Canities of scalp hairs (age)	++++ 20-30 yr.	± 40 yr.	0	++++ 2-5 mo.	+++ 20-30 yr.	Bald
Sparse sex hairs	+++	++	0	+++	+++	0
Muscular atrophy on distal parts of extremities	+++	±	0	+++	+++	0
Atrophy of the subcutaneous fat tissue	+++	±	0	+++	+++	0
Bilateral cataracts	++++ 20-30 yr.	++++ 3-4 yr.	±	0	+++ 20-30 yr.	0
Diffuse arteriosclerosis	+++	±	0	++++	++	0
Osteoporosis	+++	0	0	++	+	0
Joint deformities	+++	+	0	+++	+	0
Thyroid	+	0	0	0	+	0
Proptosis	+++	0	0	++++	0	0
Sexual underdevelopment	++++	++	0	+++	+++	0
Myotonic reaction	0	0	0	0	++	0

biopsy sections were of no help in establishing a diagnosis.

No diagnosis seems entirely explanatory of this symptom complex. An unusual case (Fig. 12) reported by Pachman[5] seems somewhat similar in nature, but was described as progressive, generalized, diffuse scleroderma with sclerodactylia and calcinosis. Photographs of his case show more involvement of the skin of the head and scalp than does our patient. That child died about one and a half years later, and an autopsy was not done. Our patient has had the advantage of superior care. Such attention may be an important factor in increasing his longevity, whereas Pachman's patient was found in a blanket-covered box behind the kitchen wood stove, and had received practically no medical supervision when first seen. Pachman's article opens with a unique description of the disease written by Ernie Pyle. Lee Miller[6] mentions it in his book, stating that it is probably

the best description of a disease written by a lay person to be found in a medical publication. In the same article is an excellent bibliography of the diffuse type of scleroderma.

In our case, at various times since infancy, the following disorders have been considered: syphilis, atopic eczema, leprosy, gout, juvenile rheumatoid arthritis (Still's disease), dermatomyositis, myositis ossificans progressiva, scleroderma, and hyperparathyroidism.

Otto Werner[7] described similar cases in his Doctor's Thesis from the Ophthalmological Clinic in Kiel, in 1904. August Rothmund[8] of Munich, also an ophthalmologist, described three cases, in 1868, under the title, "Cataracts in Association With a Peculiar Degeneration of the Skin." His cases all originated from a small mountain area in the Alps where most of the inhabitants had intermarried. He found three families in which the children had cataracts, resulting in blindness, and exhibiting skin alterations. An interesting genetic study was made on the fate of those children by R. Seefelder,[9] who investigated the same patients sixty-seven years after Rothmund's original publication. He found that the children of the three families lived to average age. Those who exhibited cataracts and had the skin lesions had not married and had no children. The normal siblings produced normal offspring. In 1934, Oppenheimer and Kugel[10] reported this condition in the American literature and renamed it "Werner's syndrome."

Thannhauser[11] has described progeria of the adult (Werner's syndrome). Table I lists the essential diagnostic features of this syndrome. Our patient, as yet, neither exhibits canities or premature alopecia, nor has he developed cataracts, diabetes, or blood vessel calcification. When an attempt is made to classify a contemporary patient under a syndrome described in patients who lived five to ten decades ago, one possibility must be considered: Patients living today probably have had the course of their chronic illness so modified by vitamin and endocrine preparations, as well as antibiotics, that some characteristics of the disease may be late in appearing, or absent.

Despite these discrepancies, there is enough similarity in the recorded cases of Werner's syndrome and our patient to justify consideration that this may represent a variant form of progeria of the adult. The latter tends to occur in siblings; the termination in abortion of all other pregnancies in this family may be significant. The syndrome probably represents an extensive germ plasma defect involving the collagen system.

Clinicians in the different specialties of dermatology, ophthalmology, endocrinology, neurology, roentgenology, pediatrics, and internal medicine may have encountered similar cases which would fit under this broader classification suggested by Thannhauser.

SUMMARY

A puzzling case is reported of extensive atrophy and sclerosis of the skin, fibrous tissue, muscle and bone, the dystrophy beginning at the age of one week and progressing for eighteen years to a profoundly disabling disorder at the present time. The difficulties of diagnostic classification are discussed.

Acknowledgment is made to Dr. Ralph Knutte for his report of the biopsy specimens, and to Dr. Daniel J. Pachman, of Chicago, and to the *American Journal of Diseases of Children*, for permission to reproduce the photograph of his patient.

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THE EFFECT OF ALLERGY MANAGEMENT ON GROWTH AND DEVELOPMENT OF ALLERGIC CHILDREN

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INTRODUCTION

A RELATIONSHIP between allergy and growth and development in children has been demonstrated.[1] In Cohen's study of allergic children in Cleveland, he noted growth failure to be two and one-half times more common in allergic children than in normal controls and also observed, "disturbed growth of the affected children as a group, even though they had continuous management of their allergy. . . ." He did, however, illustrate two case histories showing marked improvement on allergy management.[2] In order to evaluate the relationship between an adequate allergy control program and the growth patterns of allergic children, a study was made of children attending the allergy clinic at Children's Memorial Hospital in Chicago. The heights and weights of those who had been followed for a sufficiently long time were plotted on Wetzel Grids. This method was chosen because it not only evaluates physical status and body type, but distinguishes between satisfactory and unsatisfactory growth progress.[3]

METHOD OF STUDY

To insure an adequate follow-up period in the allergy clinic, the records of children in attendance during 1948 were used as source material. Only those patients who were observed for a minimum of twelve months after coming to the allergy clinic were tabulated. There were thirty-four such records available and the duration of follow-up ranged from twelve to one hundred months, averaging thirty-six months for the entire group. A total of 378 height and weight values were plotted, averaging eleven points plotted per patient, or one approximately every four months. Inasmuch as the specific diagnoses in some of the individual cases varied during the course of their observation, e.g., perennial rhinitis, seasonal hay fever, seasonal asthma, they could not be catalogued by disease alone. Twenty-six of the thirty-four cases were, however, on perennial hyposensitization indicating a predominance of pollen or mold sensitive cases. The remainder were epidermal and dust sensitive children. Undoubtedly, the regular attendance at the clinic required by the hyposensitization procedure enabled these children to provide us with much more complete records for study and, consequently, they form a disproportionately large percentage of the entire group. The ages ranged from 18 months to 11½ years at time of coming to the allergy clinic. A slight predominance of males over females was noted, 19 to 15. No correlation was made with the degree of symptomatic improvement in these cases,

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nor with other influences upon growth, e.g., nutrition or endocrine factors.

The principles of allergy management used in our clinic begin with complete skin testing of all patients with 240 antigens, both food and inhalant. The original tests are done by the scratch method, and if the patient reacts to these, the entire series is done this way. If, however, the preliminary or "scout scratch" tests are negative, the entire series is done intradermally. When the tests correlate with the clinical history, they are considered significant. The offending antigens are eliminated when possible, as with house dust and epidermals. Where elimination is impossible, as with molds and pollens, hyposensitization is carried out, using the perennial method. Positive food tests are considered to be significant only when associated with clinical symptoms.

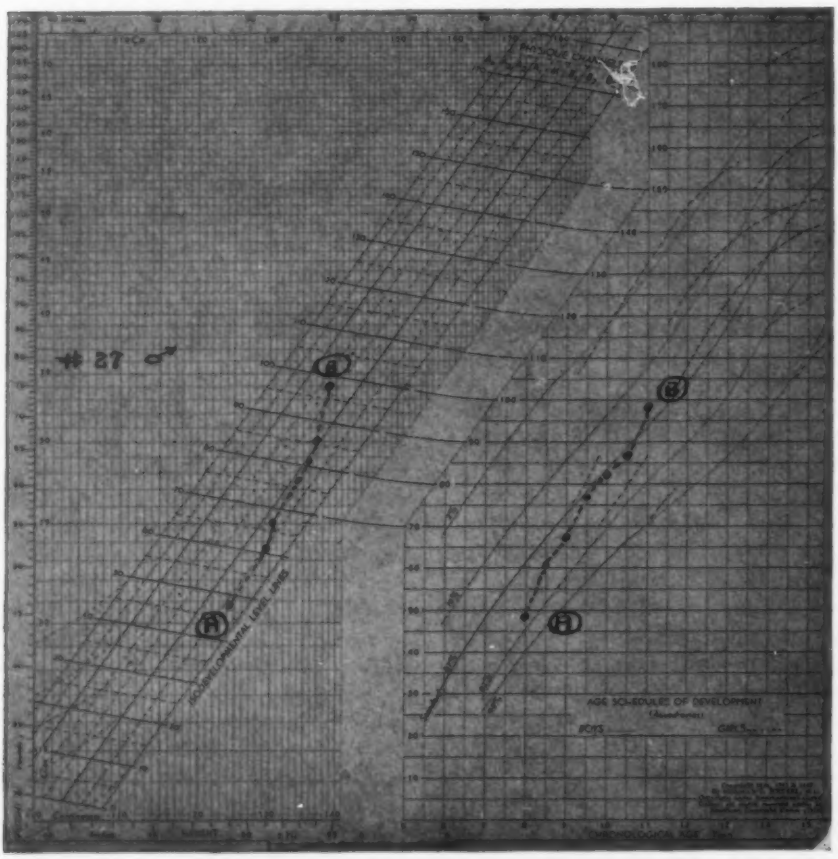

Chart 1.—*A*, Upon coming to allergy clinic in August, 1947, physique in Channel B_3 or Borderline group, with auxodrome twelve months behind 67 per cent. *B*, Last reading on Grid in June, 1950, in Channel M or Good physique with the auxodrome six months in advance of the 67 per cent standard, a total advancement of eighteen months.

Where the latter are not striking, the food is eliminated for a short period, then reintroduced in large amounts and the development of symptoms noted.

RESULTS

The method chosen for evaluating relative progress on the Wetzel Grids was that of comparing the position of the child's auxodrome, determined by his developmental level and his age, with a standard reference auxodrome, the 67 per cent auxodrome. The latter is said to indicate the levels of development which two-thirds of children should reach on or before, hence no later than, the corresponding ages to which it refers. This is a convenient reference standard by which it is possible to estimate development relative to the childhood population at large. Advancement or retardation therefrom is measured in months or fractions of a year.[3] In

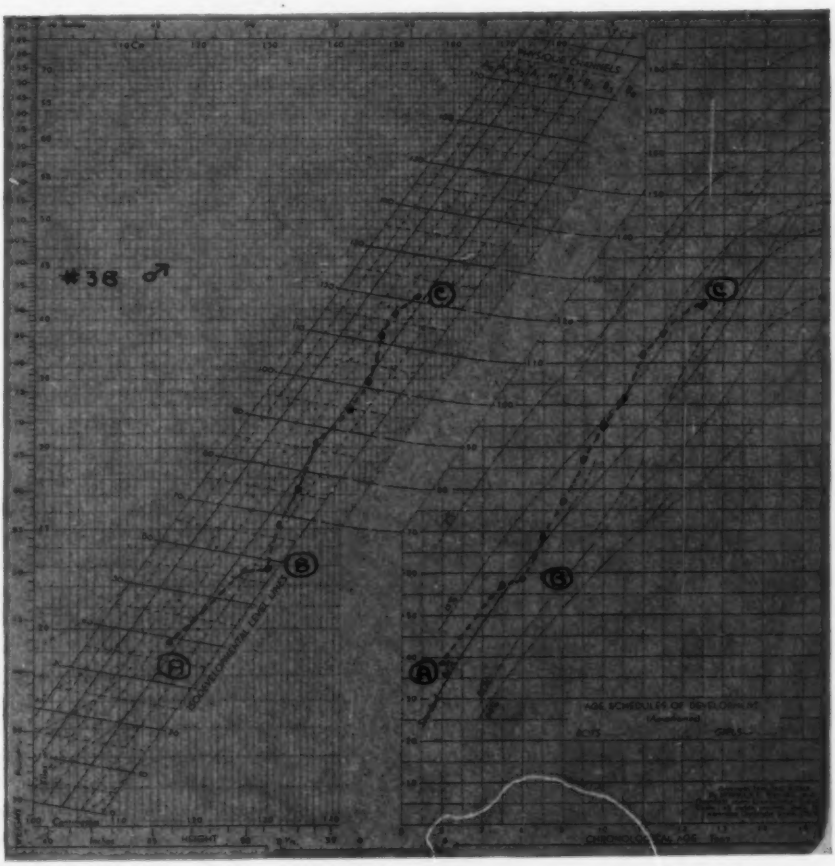

Chart 2.—*A* to *B* indicates growth failure from October, 1943, to October, 1945, shifting from Channel B_1 (Good) to B_2 (Borderline) and from a plus (+) four months auxodrome to a minus (−) four months. *B* to *C*, under allergy management to June, 1950, returning to B_1 Channel and an auxodrome of plus (+) ten months.

our study, the relative position to the standard was noted as months plus or minus at the time of coming to the allergy clinic and then compared with the last recorded measurement at the clinic.

Of the thirty-four patients (Table I), eighteen showed some degree of improvement, fourteen continued to advance in an acceptable manner, while two showed very slight deceleration. The thirty-four cases as a group showed a slight advancement over the entire period, the last auxodrome showing a 4.4 months' advance over the first. Broken down individually, there were seven cases with two to six months' advancement, termed slight improvement; eight cases with six to twelve months' advancement, termed moderate improvement; and four cases with greater than twelve months' advancement or marked improvement (Charts 1 and 2). Fourteen of the cases showed a deviation of from plus 2 to minus 2 months from their original position and these were classified as having no change in growth pattern.

TABLE I

Total cases	34	Cases with no change	14
Improved	18	Continued satisfactory	9
No change	14	Improved over previous	3
Impairment	2	Inadequate previous records	2

These latter fourteen cases were further studied with regard to their progress rates prior to coming to the allergy clinic. This was done by noting the rate of advancement of developmental levels per months, one per month being standard. Nine of the patients advanced at this minimum rate both before and after allergy management and hence their progress is deemed to be continued satisfactory. Three patients were not advancing satisfactorily prior to allergy control, but did so subsequently, hence are improved. In the two remaining cases, insufficient data prior to the patient's coming to the allergy clinic were available to make an adequate appraisal.

Only two cases showed a deceleration of expected advancement, one being of four months, another of three months; consequently, thirty-two of the thirty-four cases showed satisfactory development in the allergy clinic; twenty-one were improved and nine continued to develop at a satisfactory rate, while two cases showed impairment of development.

DISCUSSION

These results would indicate that there has been a moderate, though not striking, improvement in the overall growth and development patterns of the children studied here as contrasted with the anticipated incidence of growth failure. In discussion of factors influencing growth, chronic illness and recurrent respiratory infection are commonly mentioned as being important.[4] Insofar as these chronic illnesses or infections may be related to allergy, control of the allergy would understandably influence growth in these cases. More striking are the noted sequelae of prolonged or severe asthma in children, thirty-four of 100 cases reported by Peshkin showing changes of varying degrees of chronic bronchitis, emphysema, or bronchiectasis. Twelve of these thirty-four showed significant chest deformities.[5] Holt and McIntosh, in speaking of sequelae of asthma, refer to interference with nutrition leading

to permanent stunting of growth and delayed puberty. Brennemann lists chronic bronchitis, chronic sinusitis, emphysema, and chest deformities as complications of asthma and goes on further to state that "recurrent attacks of asthma are invariably accompanied by some degree of bronchitis and cause a hyperirritability of the bronchial mucus membrane which may become chronically infected as a result," with ensuing "peribronchial fibrosis and occasional bronchiectasis" in some cases. The statement is also made that "if the asthma in children is relieved one can expect the lungs to be restored to normal and even a considerable reduction in the deformity of the chest" as contrasted with the less favorable prognosis in adults.

Although present-day allergy management is not without limitations, most authorities agree that the increasing progress of allergic manifestations can be arrested and severe asthma definitely minimized or eliminated in 75 to 85 per cent of cases. In this way, certain predisposing factors to chronic respiratory infection or malformation of the respiratory tree may be minimized in susceptible individuals.

SUMMARY

1. A study was made of the effect of allergy management on the growth and developmental progress of thirty-four allergic children as followed for periods ranging from twelve to one hundred months.

2. Thirty-two of the thirty-four children advanced at satisfactory or improved rates, as determined by the Wetzel Grids, during the periods of their allergy management.

3. In these children studied, allergy management was attended by definite, though not marked, improvement in growth, as contrasted with an anticipated increased incidence of growth failure.

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THE TREATMENT OF INFANTILE DIARRHEA WITH A NEW COMBINATION OF ANTIBIOTICS

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GREAT progress has been achieved in the treatment of diarrhea in infants and children during the past fifteen years. The recognition and application of basic principles of fluid balance and electrolyte metabolism[1, 2, 3, 4, 5] have been, perhaps, the most revolutionary contributions to the modern management of such disorders. The introduction of the sulfonamides and of the antibiotic drugs, however, afforded a direct approach to treating the causes of the fluid and electrolyte disturbances, i.e., the infected and inflamed gastrointestinal tract.

The present study concerns itself with the treatment of infantile diarrhea with a combination of two new antibiotics, neomycin and bacitracin. The isolation of bacitracin[6] presented a new drug which in vitro and in vivo showed promising action against gram-positive cocci and bacteria, a few larger viruses, and *Endamoeba histolytica*.[7] Neomycin, discovered by Waksman,[8] appeared to be effective against few gram-positive but many gram-negative bacteria, the tubercle bacillus, and *E. histolytica*.[7] A synergistic effect is achieved when neomycin and bacitracin are administered simultaneously.[9] The combination of neomycin and bacitracin will henceforth be referred to as "Neobacin." In view of the favorable results obtained in vitro and in experimental animals, it was felt that a clinical study should be undertaken to determine the effectiveness of Neobacin against infantile diarrhea as compared with previously used treatments.

The study consisted of a series of fifty-three infants under 1 year of age who were either admitted to the hospital because of diarrhea or developed such a condition while hospitalized for a different reason.

The stools of all patients were cultured for pathogenic bacteria and examined for protozoa.[10] No viral studies were performed. Rectal swabs were placed in tetrathionate broth, and after twenty-four hours' incubation streaked to Levine's eosin methylene blue agar, sodium azide blood plate, and Shigella-Salmonella (S.S.) agar. After twenty-four hours, two more S.S. plates were inoculated from the tetrathionate broth. The parasitologic examination was carried out by examining fresh stools within twenty minutes after evacuation, followed by zinc flotation and hematoxylin-stained permanent slides.

All patients treated with Neobacin as well as the controls received weak tea or water by mouth for the first twelve to twenty-four hours. This was followed by the addition of a formula consisting of one part of boiled skim milk to one part of water. Whole boiled skim milk to which Casec was added was given to the

From the Children's Division and from the Hektoen Institute for Medical Research of the Cook County Hospital.

infants within the next twenty-four to forty-eight hours. After a period of two to three days, the patients received a dilute evaporated milk formula to which carbohydrate was gradually added. One teaspoon of Kaopectate q. 4 h., and 5 gr. of calcium lactate t.i.d. were given to all patients who had liquid stools.

Seriously ill patients constituted 54 per cent of the infants. They were severely dehydrated and were given parenteral fluids, plasma, Amigen, and blood transfusions. Three of them had hypopotassemia and received, therefore, potassium chloride, 1 Gm. daily subcutaneously for two to three days.

Thirty-two of the infants were started on sulfadiazine (1 gr. per pound of body weight daily), streptomycin (100,000 to 200,000 units q. 6 h. orally), and procaine penicillin (150,000 to 300,000 units daily intramuscularly) alone or in combinations. Neobacin* was given to the other infants in dosage of one tablet q. 6 h. orally. Three who had amebiasis received two tablets of Neobacin q. 6 h. Five of the patients were on a different schedule. They received 2,500 units of neomycin and bacitracin each, q. 6 h. orally.

As the study progressed, it became apparent that twenty-three infants of the control group were doing poorly on the sulfadiazine, streptomycin, and penicillin combinations. It was decided, therefore, to place them later on Neobacin therapy.

RESULTS

Table I demonstrates the study of nine cases of amebiasis in infants between 2 and 9 months of age. Five were admitted to the hospital with severe diarrhea, dehydration, and acidosis. Three had chronic persistent diarrhea with intermittent periods of dehydration. One had a history of cramps and irritability without diarrhea.

Six of the nine infants had been treated with sulfadiazine, streptomycin, and penicillin alone or in combinations before *E. histolytica* was isolated from the stools. The results were poor. One infant had been previously treated with bacitracin alone. Although the diarrhea subsided under this treatment, *E. histolytica* was still present prior to Neobacin therapy.

The dosage of Neobacin used in seven of the nine patients was one tablet q. 6 h. for fourteen days. Three of them required a second course of Neobacin, two tablets q. 6 h. for fourteen days. Two infants were on different treatment schedules, having received 2,500 units each of neomycin and bacitracin q. 6 h. for five days.

After the institution of Neobacin therapy, the diarrhea subsided in one to four days, on the average in 1.86 days. Two of the infants continued to harbor *E. histolytica* in their stools, but did not have diarrhea. All patients were proctoscoped, and showed considerable improvement after the treatment.

Table II represents nine infants between three weeks and 10 months of age with acute diarrhea. Seven of these were dehydrated and required parenteral fluids and blood transfusions on admission.

Five had *Proteus morganii* in their stools on admission. One of them con-

*Each tablet contained 10,000 units of neomycin and 2,000 units of bacitracin and was supplied through the courtesy of the Commercial Solvents Co., Terre Haute, Ind.

TABLE I. AMEBIASIS

CASE	CLINICAL SUMMARY	STOOL EXAMINATION FOR E. HISTOLYTICA	TREATMENT	COURSE
1. R. A. 5 mo.	Adm. on 6/17/50 with a diagnosis of bronchopneumonia and eczematoid dermatitis. Treated with sulfadiazine, streptomycin, and procaine penicillin from 6/17 to 6/23. On 6/26/50 developed generalized convulsions, temp. of 103.2° F. and diarrhea.	6/20 No pathogens cultured from stool 6/23 *E. histolytica* found 7/8, 7/10, 7/12 *Negative* for *E. histolytica*	Procaine penicillin, 6/26 to 6/29, 300,000 U. daily. Streptomycin 200,000 U. q. 6 h. Neomycin 4,000 U. q. 6 h. I.M. from 6/26 to 6/27. Neobacin tab. 1 q. 6 h. 6/27 to 6/30.	Afebrile by 6/28. Required parenteral fluids 6/28, 6/29 and 6/30. No stools from 6/28 to to 7/1. Proctoscopy normal on 7/10. Normal stools by 7/2. Discharged 7/16
2. M. L. 5 Mo.	Adm. on 6/9/50 because of cramps and irritability. History of melena at 2 weeks of age. No diarrhea present.	6/12 *E. histolytica* found 7/3, 7/5, 7/10 Negative for *E. histolytica*	Neobacin tab. 1 q. 6 h. 6/15 to 6/30.	On 7/13 proctoscopy was normal. Discharged on 7/18.
3. M. C. 3 mo.	Adm. on 5/14/50 because of diarrhea and vomiting. On 5/31/50 *E. histolytica* isolated from stools. Treated with bacitracin 10,000 b.i.d. orally from 5/31 to 6/14. *E. histolytica* found in stool after therapy.	6/13 *E. histolytica* 7/10, 7/14, 7/17, 8/5, 8/3, 8/9 Negative for *E. histolytica*	Neobacin tab. 1 q. 6 h. from 6/23 to 7/6. Neobacin tab. 2 7/17 to 8.2.	On 7/13, proctoscopy showed multiple areas of petechiae, ulceration, edema, and hyperemia of bowel. On 8/12 proctoscopy showed marked improvement. Discharged on 8/15.
4. R. D. 7 mo.	Adm. on 4/7/50 because of severe atopic eczema. On 5/28/50 developed a diarrhea. Treated with procaine penicillin and sulfadiazine from 5/28 to 6/4. Still having few semiliquid stools.	5/31 *E. histolytica* 6/21 Negative for *E. histolytica* 6/29 *E. histolytica* 7/10 *E. histolytica* 8/4 *E. histolytica* isolated	Neobacin tab. 1 q. 6 h. from 6/4 to 6/18. Neobacin tab. 2 q. 6 h. from 7/19 to 7/31.	Normal stools by 6/5. On 6/15 proctoscopy revealed edema and hyperemia of bowel with excess mucus. On 8/3 mucosa of bowel markedly improved. One localized area of petechial hemorrhage. Stool positive for *E. histolytica*.
5. C. Q. 3 mo.	Adm. on 6/5/50 because of diarrhea for 3 days. Convulsing, dehydrated, acidotic. Treated with procaine penicillin and streptomycin from 6/5 to 6/6. Continuing to have liquid stools.	6/7 *E. histolytica* 7/10 *E. histolytica* 7/4, 7/17, 8/2, 8/4, 8/10 Negative for *E. histolytica*	Neobacin tab. 1 q. 6 h. 6/6 to 6/11, 6/15 to 6/30, 7/16 to 7/30.	Diarrhea subsided by 6/9. Required S.Q. fluids until 6/11. Proctoscopy on 6/15 revealed bleeding rectal mucosa. On 7/20 some improvement noted on proctoscopy, but edema and inflammation of mucosa still present. On 8/12 proctoscopy revealed normal mucosa. Discharged 8/12.

6. T. O. 3 mo.	Adm. on 6/19/50 because of diarrhea and fever for 3 days. Temp. 100.4° F., dehydrated.	6/19 *E. histolytica* 7/18, 7/19, 7/21 Negative	Procaine penicillin 150,000 U. q. A.M. 6/19 to 6/22. Neobacin tab. 1 q. 6 h. 6/19 to 7/3.	Given blood and fluids on 6/19 and 6/20. Afebrile by 6/21. Diarrhea subsided by 6/23.
7. J. G. 2 mo.	Adm. on 1/30/50 because of diarrhea. had chronic persistent liquid to semiliquid stools with dehydration up to 2/15/50. Had previous treatment with sulfadiazine, streptomycin, and procaine penicillin. Fluids given almost every other day until 2/15/50.	2/6 *E. histolytica* 2/14, 2/28, 3/2, 3/13, 3/16 Negative	Neomycin and bacitracin 2,500 U. of each q. 6 h. 2/15 to 2/20.	Normal stools by 2/16. No fluids necessary after therapy completed. Made good weight gain with eventual discharge.
8. L. M. 2 mo.	Adm. on 12/22/49 because of fever and diarrhea. Continued to run chronic intermittent liquid to semiliquid stools with chronic dehydration. Had been treated with sulfadiazine, streptomycin, and procaine penicillin. Parenteral fluids given almost daily.	2/14 *E. histolytica* 3/2, 3/5, 3/6, 3/8 Negative	Neomycin and bacitracin 2,500 U. of each q. 6 h. 2/15 to 2/20.	Normal stools 2/16. No fluid necessary after therapy. Made good weight gain after therapy. No relapse noted in 1 month follow-up.
9. K. B. 9 mo.	Adm. 8/25/50 because of diarrhea for 4 days. Chronic diarrhea and dehydration to and including 9/5/50. Had been treated with sulfadiazine and penicillin and required daily fluids up to 9/5/50.	8/31 *E. histolytica* isolated 9/21 *E. histolytica* isolated 9/28 *E. histolytica* isolated	Neobacin tab. q. 6 h. 9/5 to 9/8. Neobacin tab. 2 q. 6 h. 9/8 to 9/18.	Normal stools by 9/7. Daily fluids discontinued by 9/7. Made good weight gain. Stool still positive for *E. histolytica*.

TABLE II. INFANTILE DIARRHEA TREATED WITH NEOBACIN

CASE	CLINICAL SUMMARY	STOOL CULTURE	TREATMENT	COURSE	WEIGHT
1. D. B. 6 mo.	Adm. 5/25/50 because of diarrhea for 6 days and weight loss of 2 lb. 10 oz. in 7 days. Temp. of 101.2° F. Dehydrated.	5/25 Negative 6/5 *Pr. morganii*	Neobacin tab. 1 q. 6 h. 5/25 to 5/31.	Normal stools 5/29. Discharged 6/10.	5/25 10 lb. 7 oz. 6/6 11 lb. 13 oz. 6/10 12 lb. 3 oz.
2. K. C. 10 mo.	Adm. 6/3/50 because of diarrhea and vomiting for 1 week. Lost 2 lb. in 4 days. Dehydrated on admission.	5/31 *Pr. morganii* 6/5 *Pr. morganii* 6/12 *Pr. morganii*	Neobacin tab. 1 q. 6 h. 6/3 to 6/9.	Daily fluids to 6/5. Diarrhea subsided by 6/6. Discharged 6/13.	6/3 16 lb. 9 oz. 6/12 17 lb. 9 oz.
3. C. D. 2 mo.	Adm. 6/19/50 because of diarrhea for 2 days. Treated with Kaopectate and tea 6/19 to 6/23 when began to develop liquid stools.	6/19 *Pr. morganii* 6/22 Negative 6/18 *Ps. aeruginosa*	Neobacin tab. 1 q. 6 h. 6/23 to 6/27.	Normal stools 6/24. Discharged 6/28.	6/19 8 lb. 4 oz. 6/26 8 lb. 8 oz.
4. K. H. 3 mo.	Adm. 6/20/50 because of diarrhea and dehydration. Temp. 100° F.	6/20 *Pr. morganii* 6/28 Negative	Neobacin tab. 1 q. 6 h. 6/20 to 6/26.	Almost daily fluids to 6/25. Normal stools by 6/25. Discharged 6/28.	6/20 8 lb. 11 oz. 6/28 9 lb. 6 oz.
5. T. H. 1 mo.	Adm. 6/26/50 because of diarrhea for 2 days. Dehydrated on admission.	6/26 *Pr. morganii* 6/29 Negative 7/1 Negative	Neobacin tab. 1 q. 6 h. 6/26 to 6/30.	Daily fluids to 6/26. Normal stools by 6/27. Discharged 7/7.	6/20 6 lb. 11 oz. 7/3 7 lb. 6 oz.
6. B. R. 3 wk.	Adm. 5/10/50 because of premature synostoses. Developed diarrhea on 6/15/50.	6/15 Negative 7/2 *Pr. morganii*	Neobacin tab. 1 q. 6 h. 6/15 to 6/24.	Fluids given 6/15 and 6/16. Normal stools by 6/22 Discharged 7/15.	6/15 5 lb. 9 oz. 7/5 6 lb. 14 oz.
7. M. S. 3 mo.	Adm. 6/28/50 because of diarrhea for 9 days. Dehydrated on admission.	6/28 Negative	Neobacin tab. 1 q. 6 h. 6/28 to 7/1.	Normal stools 7/1. Discharged 7/11.	6/28 9 lb. 10 oz. 7/7 10 lb. 5 oz.
8. R. W. 2 mo.	Adm. 6/28/50 because of chronic diarrhea for 3 weeks. Dehydrated on admission.	6/28 *Pr. morganii*	Neobacin tab. 1 q. 6 h. 6/28 to 7/3.	Normal stools by 7/3. Discharged 7/7.	6/28 9 lb. 7/5 10 lb. 4 oz.
9. J. W. 1 mo.	Adm. 5/8/50 with multiple congenital anomalies. Developed diarrhea on 6/17/50.	6/17 Negative	Neobacin tab. 1 q. 6 h. 6/17 to 6/25.	Fluids and blood given 6/22. Normal stools 6/21.	6/17 6 lb. 3 oz. 6/30 6 lb. 7 oz.

tinued to harbor *Pr. morganii* and another *Pseudomonas aeruginosa* after Neobacin therapy, though diarrheic and general symptoms disappeared during the course.

None of these infants had previous therapy. Neobacin was administered one tablet q. 6 h. for four to seven days. The results were satisfactory. The average duration of the diarrhea was 3.22 days. No recurrences were noted after Neobacin treatment.

Table III shows diarrhea in thirteen infants between 11 days and 11 months of age who had been previously treated with sulfadiazine, streptomycin, and penicillin alone or in combinations, with poor results. Three of the patients showed an encouraging initial response while on such treatment but had a recurrence of the diarrhea in spite of the medication.

Six of these patients harbored *Ps. aeruginosa* and one infant had *Pr. morganii* in the stools before and after therapy. Five of the patients had persistently negative stool cultures. All of the patients were asymptomatic after treatment with Neobacin.

Ten infants in this group were given Neobacin 1 tablet q. 6 h. from four to seven days. To three patients, 2,500 units each of neomycin and bacitracin q. 6 h. for four days were given. The average duration of the diarrhea was 2.8 days.

Table IV represents thirteen infants between 9 days and 9 months of age with diarrhea. Four had been treated with sulfadiazine, streptomycin, and penicillin unsuccessfully. After this, the patients were treated with Neobacin and penicillin. Penicillin was used because of complicating upper respiratory tract infections or bronchopneumonia.

Two infants had Paracolobactra and two had *Pr. morganii* before and after Neobacin treatment. Six patients had persistently negative stool cultures.

The dosage of Neobacin was one tablet q. 6 h. from four to nine days. Procaine penicillin was given, 150,000 to 300,000 units intramuscularly, from two to nine days. The average duration of the diarrhea was four days. No recurrences were noted after this treatment.

Table V represents nine patients between 2 weeks and 10 months of age with acute diarrhea. These infants were treated initially with sulfadiazine, streptomycin, and penicillin alone or in combinations.

Three infants had *Pr. morganii*, three had Paracolobactra, and one had *Pr. vulgaris* in their stools.

The average duration of diarrhea in these patients was 6.44 days. Two had relapses and required further treatment.

DISCUSSION

One of the problems frequently encountered in the study of diarrheic disorders is the role played by members of the Proteus, Paracolobactrum (paracolon) and Pseudomonas genera of microorganisms, especially in infants and children. Neter and Clark[11] felt that Paracolobactra may be the primary cause of diarrhea in infants and children but stated that these organisms may be present as saprophytic, harmless organisms, or be associated with enteric pathogens and play a secondary part as incitants of diarrheal diseases. Felsenfeld and Young[12] showed a higher incidence of Protei and Paracolobactra in adults with diarrhea than in healthy individuals. Levinson and Rayeraft[13]

TABLE III. INFANTILE DIARRHEA PREVIOUSLY TREATED WITH SULFADIAZINE, STREPTOMYCIN, AND PENICILLIN

	CLINICAL SUMMARY	STOOL CULTURE	TREATMENT	COURSE	WEIGHT
1. H. B. 4 yr.	Adm. 5/21/50 because of diarrhea of 5 days' duration. Temp. 101.4° F. Had pharyngitis. Treated with sulfadiazine, streptomycin, and penicillin. Afebrile on 5/25/50 but diarrhea persisted.	6/6 *Pr. morganii*	Neobacin tab. 1 q. 6 h. 5/25 to 5/31.	Normal stools by 5/28. Discharged 5/31.	
2. G. P. 3 mo.	Adm. 5/31/50 because of diarrhea for 1 week. Dehydrated on admission. Treated with sulfadiazine, streptomycin, and penicillin to 6/1/50.	5/31 *Pr. morganii* 6/8 *Ps. aeruginosa* 6/12 *Ps. aeruginosa*	Neobacin tab. 1 q. 6 h. 6/1 to 6/8.	Normal stools by 6/6. Discharged 6/14.	5/31 16 lb. 10 oz. 6/14 17 lb. 10 oz.
3. C. P. 4 mo.	Adm. 6/28/50 because of diarrhea for 4 days. Dehydrated. Treated with sulfadiazine, streptomycin, and penicillin from 6/28 to 7/12. Continued to have semi to liquid stools.	6/28 *Ps. aeruginosa*	Neobacin tab. 1 q. 6 h. 7/12 to 7/16.	Normal stools by 7/14. Discharged 7/25.	6/28 11 lb. 3 oz. 7/15 11 lb. 7 oz.
4. L. H. 2 mo.	Adm. 1/18/50 because of diarrhea, melena, and hematemesis. Developed jaundice on 2/1/50. Treated with sulfadiazine, streptomycin, and penicillin.	1/18 Negative 2/4 *Ps. aeruginosa* 2/6 Negative 2/15 *Ps. aeruginosa*	Neomycin and bacitracin 2,500 U. q. 6 h. 2/15 to 2/20.	Soft acholic stools by 2/16.	2/10 7 lb. 9 oz. 2/20 8 lb.
5. J. B. 1 mo.	Adm. 1/30/50 because of diarrhea since birth. Treated with sulfadiazine, streptomycin, and penicillin. Continued to have liquid stools to 2/19/50.	1/30 Negative 2/21, 3/2. *Ps. aeruginosa*	Neomycin and bacitracin 2,500 U. q. 6 h. 2/19 to 2/22.	Normal stools by 2/20.	2/17 6 lb. 15 oz. 3/6 7 lb. 11 oz.
6. C. J. 7 mo.	Adm. 1/7/50 because of diarrhea. Treated with sulfadiazine, streptomycin and penicillin. Chronic diarrhea persists.	2/14, 2/15 *Ps. aeruginosa* 2/21 Negative 3/5 *Ps. aeruginosa*	Neomycin and bacitracin 2,500 U. q. 6 h. 2/15 to 2/18.	Normal stools by 2/16.	2/10 10 lb. 14 oz. 2/20 11 lb. 10 oz. 3/6 13 lb. 4 oz.
7. C. C. 4 mo.	Adm. 5/15/50 with diagnosis of Coffey's syndrome. Developed diarrhea on 5/30/50. Treated with sulfadiazine and streptomycin.	6/2 Paracolon 6/3 Paracolon 6/5 *Ps. aeruginosa*	Neobacin tab. 1 q. 6 h. 6/2 to 6/6.	Required fluids 6/3. Normal stools by 6/6. Discharged 6/25.	6/2 10 lb. 9 oz. 6/8 10 lb. 15 oz. 6/25 11 lb. 11 oz.

8. G. F. 11 mo.	Adm. 6/1/50 because of nasopharyngitis and draining right ear. Also had bilateral bronchopneumonia. Temp. of 102.2° F., respirations 60, pulse 180. Treated successfully with penicillin, sulfadiazine, and streptomycin from 6/1 to 6/14. On 6/9/50 developed diarrhea and a hypopotassemia.	6/1, 6/8, 6/12 Negative	Neobacin tab. 1 q. 6 h. 6/14 to 6/18.	Potassium deficiency corrected with fluids. Normal stools by 6/16. Discharged 6/19.	6/1 6/19	16 lb. 15 oz. 16 lb. 4 oz.
9. R. F. 2½ mo.	Adm. 5/22/50 with history of diarrhea for 1 day. Dehydrated and acidotic on adm. Treated with sulfadiazine, streptomycin, and penicillin from 5/22 to 5/25 with persistence of liquid stools.	5/25, 6/5, 6/8 Negative	Neobacin tab. 1 q. 6 h. 5/25 to 5/31.	Stools became formed by 5/27. Normal stools by 5/29. Discharged 6/13.	5/22 6/13	5 lb. 15 oz. 7 lb. 1 oz.
10. R. H. 3 mo.	Adm. 5/19/50 because of diarrhea for 3 days. Treated successfully with sulfadiazine, streptomycin, and penicillin from 5/19 to 5/26. On 6/1/50 developed relapse of diarrhea and became dehydrated.	5/19, 5/31, 6/1 Negative	Neobacin tab. 1 q. 6 h. 6/1 to 6/8.	Considerable improvement in 24 hr. Normal stools by 6/4. Discharged 6/12.	5/19 6/1 6/12	9 lb. 10 oz. 9 lb. 8 oz. 10 lb. 7 oz.
11. L. S. 3 da.	Adm. 6/20/50 because of diarrhea. Treated with oral streptomycin 6/20 to 6/25 with apparent good results. On 6/28/50 developed liquid stools again and went into shock. Blood, fluids, stimulants, and oxygen given.	6/20 Negative	Neobacin tab. 1 q. 6 h. 6/28 to 7/8.	Had only 2 semiliquid stools from 6/29 to 7/2. Normal stools by 7/3. Discharged 7/21.	6/20 6/28 7/21	4 lb. 12 oz. 4 lb. 8 oz. 5 lb. 1 oz.
12. M. W. 6 wk.	Adm. 5/26/50 because of diarrhea for 5 days. Treated with penicillin, sulfadiazine, and fluids up to 6/6/50 when therapy was discontinued due to persistence of diarrhea. Dehydrated.	5/29 *Ps. aeruginosa* 6/5 *Ps. aeruginosa* 6/6 *E. Coli* 6/12 *Ps. aeruginosa*	Neobacin tab. 1 q. 6 h. 6/6 to 6/10.	Fluids and blood given 6/6. Normal stools by 6/9. Discharged 6/14.	6/6 6/14	7 lb. 9 oz. 7 lb. 14 oz.
13. R. W. 2 wk.	Adm. 5/21/50 because of diarrhea for 4 days. Dehydrated and acidotic. Treated with sulfadiazine, streptomycin, penicillin, and fluids daily from 5/21 to 6/1 with persistence of liquid to semiliquid stools.	5/29, 6/5, 6/16 *Ps. aeruginosa*	Neobacin tab. 1 q. 6 h. 6/1 to 6/8.	Fluids given to 6/3. Normal stools by 6/5. Discharged 6/14.	6/1 6/5 6/14	5 lb. 10 oz. 6 lb. 6 lb.

TABLE IV. INFANTILE DIARRHEA TREATED WITH NEOBACIN AND PROCAINE PENICILLIN

CASE	CLINICAL SUMMARY	STOOL CULTURE	TREATMENT	COURSE	WEIGHT
1. B. J. 9 da.	Adm. 6/17/50 because of diarrhea for 2 days. Mild dehydration on adm. Treated with sulfadiazine, streptomycin, and penicillin with good response. Two days after therapy stopped 6/29/50, developed liquid stools. Temp. 102.2° F.	6/17 Negative 6/19 Paracolon 6/29 Paracolon	Procaine penicillin 150,000 U. daily I.M. 6/29 to 7/6. Neobacin tab. 1 q. 6 h. 6/29 to 7/6.	Afebrile 6/30. Normal stools by 7/2. Discharged 7/15.	6/17 6 lb. 1 oz. 7/15 5 lb. 15 oz.
2. C. W. 4 mo.	Adm. 6/10/50 because of failure to gain weight and malnutrition. Also had bilateral bronchopneumonia on admission. Further work-up revealed rickets. Treated with sulfadiazine and penicillin. Developed diarrhea on 6/15/50. Sulfadiazine discontinued.	6/10 Negative 6/30 Negative	Neobacin tab. 1 q. 6 h. 6/15 to 6/24. Procaine penicillin 150,000 U. daily I.M. 6/15 to 6/24.	Required parenteral fluids from 6/15 to 6/17. Normal stools by 6/18. Discharged 6/30.	6/10 9 lb. 3 oz. 6/15 8 lb. 8 oz. 6/28 9 lb. 7 oz.
3. T. B. 8 mo.	Adm. 6/6/50 because of diarrhea and lethargy for 2 days. Temp. 102.6° F. on adm. Treated with sulfadiazine and penicillin, later intramuscular and oral streptomycin given with persistence of liquid stools to 6/22. All therapy discontinued except penicillin.	6/19 Negative 6/22 Negative	Neobacin tab. 1 q. 6 h. 6/21 to 6/27. Procaine penicillin 300,000 U. daily I.M. 6/16 to 6/25.	Normal stools by 6/24. Discharged 7/5.	6/16 18 lb. 6/23 18 lb. 5 oz. 7/1 18 lb.
4. C. C. 5 mo.	Adm. 6/15/50 because of diarrhea for 3 days and convulsions. Temp. 104.2° F., pulse 180, resp. 50. Treated with fluids and blood.	6/15 Negative 6/19 *Ps. aeruginosa*	Neobacin tab. 1 q. 6 h. 6/15 to 6/20. Neomycin 5,000 U. q. 6 h. I. M. 6/15 to 6/20. Procaine penicillin 150,000 U. daily I.M. 6/15 to 6/20.	Afebrile by 6/18. Formed stools by 6/16. Normal stools by 6/19 Discharged 6/22.	6/15 14 lb. 5 oz. 6/22 16 lb. 2 oz.
5. M. C. 9 mo.	Adm. on 6/19/50 because of diarrhea for 3 days. Temp. 103° F. Dehydrated otitis media and pharyngitis.	6/22 Negative 6/23 to 6/26 *P. morganii* and *Ps. aeruginosa* 6/28 Negative	Neobacin tab. 1 q. 6 h. 6/19 to 6/26. Procaine penicillin 300,000 U. daily I.M. 6/19 to 6/24.	Afebrile by 6/21. Fluids and blood daily to 6/21. Normal stools by 6/24. Discharged 6/28.	6/19 16 lb. 13 oz. 6/28 18 lb. 8 oz.
6. S. G. 2 mo.	Adm. 6/13/50 because of diarrhea for 1 week. Temp. 105.4° F. Dehydrated and cyanotic.	6/14 *Pr. morganii*	Neobacin tab. 1 q. 6 h. 6/14 to 6/20. Procaine penicillin 300,000 U. daily I.M. 6/13 to 6/20.	Required blood and fluids 6/13 and 6/15 Normal stools 6/17. Discharged 6/23.	6/13 6 lb. 8 oz. 6/23 7 lb. 3 oz.

7. L. J. 3 mo.	Adm. 6/15/50 because of diarrhea and upper respiratory infection for 4 days not responding to penicillin. Temp. 101° F. Markedly dehydrated, semicomatose.	6/15 Paracolon 6/28 Paracolon	Neobacin tab. 1 q. 6 h. 6/15 to 6/20. Procaine penicillin 150,000 U. daily I.M. 6/15 to 6/20.	Fluids 6/15 and 6/16. Afebrile by 6/17. Normal stools by 6/20. Discharged 6/28.	6/15 6/28	7 lb. 9 oz. 9 lb. 11 oz.	
8. R. M. 7 mo.	Adm. 6/12/50 because of diarrhea for 1 day and upper respiratory infection 3 days. Temp. 101° F. Acutely ill. Nasopharyngitis.	6/12 *Pr. morganii* *E. coli*	Neobacin tab. 1 q. 6 h. 6/12 to 6/17. Procaine penicillin 6/12 to 6/16 150,000 U. daily I.M.	Fluids given to 6/14. Afebrile by 6/14. Normal stools 6/16. Discharged 6/23.	6/12 6/23	9 lb. 9 oz. 9 lb. 10 oz.	
9. B. N. 1 mo.	Adm. 5/11/50 because of upper respiratory infection. Treated with penicillin. On 6/17/50 developed diarrhea and became dehydrated.	6/8 Negative 6/14, 6/19 *Ps. aeruginosa*	Neobacin tab. 1 q. 6 h. 6/7 to 6/13. Procaine penicillin 150,000 U. daily I.M. 6/7 to 6/13.	Fluids given 6/7 to 6/9. Normal stools by 6/12. Discharged 7/4.	5/11 6/7 6/15	7 lb. 7 lb. 5 oz. 8 lb. 10 oz.	
10. B. R. 3 mo.	Adm. 6/26/50 because of diarrhea and vomiting 1 day. Markedly dehydrated.	6/26 Negative	Neobacin tab. 1 q. 6 h. 6/26 to 7/4. Procaine penicillin 150,000 U. daily I.M. 6/26 to 6/28.	Required fluids to 6/28. No stools from 6/28 to 7/1. Normal stools by 7/3.	6/26 7/7	10 lb. 10 oz. 11 lb. 1 oz.	
11. B. S. 8 mo.	Adm. 6/19/50 because of diarrhea for 1 day. Temp. 100.6° F. Treated with Kaopectate tea for 2 days with persistence of liquid stools.	6/19 Negative 6/21 *Ps. aeruginosa*	Neobacin tab. 1 q. 6 h. 6/22 to 6/26. Procaine penicillin 150,000 U. daily I.M. 6/23 to 6/25.	Developed pharyngitis 6/23. Afebrile 6/24. Normal stools 6/24. Discharged 6/30.	6/19 6/30	12 lb. 13 oz. 12 lb.	
12. W. T. 3 wk.	Adm. on 6/7/50 because of skull fracture right frontal bone. Developed diarrhea on 6/6/50. Treated with oral streptomycin, sulfadiazine to 6/22. Developed fever 101° F. on 6/21 and treated with penicillin with persistence of diarrhea.	6/19, 6/22, 6/26, 6/28 Negative	Neobacin tab. 1 q. 6 h. 6/22 to 6/26. Procaine penicillin 150,000 U. daily I.M. 6/21 to 6/24.	Afebrile by 6/24. Required fluids and blood from 6/21 to 6/23. Normal stools by 6/25. Discharged 6/28.			
13. R. T. 8 mo.	Adm. 6/20/50 because of diarrhea and vomiting for 3 days. Temp. 103.4° F. on admission.	6/26 Negative	Neobacin tab. 1 q. 6 h. 6/26 to 7/6. Procaine penicillin 150,000 U. daily I.M. 6/26 to 7/6. Neomycin 3,000 U. q. 6 h. I.M. 6/26 to 6/29.	Afebrile by 6/29. Fluids daily to 6/29. Normal stools by 7/3.	6/26 7/12	13 lb. 12 oz. 13 lb. 12 oz.	

TABLE V. INFANTILE DIARRHEA TREATED WITH SULFADIAZINE, STREPTOMYCIN, AND PROCAINE PENICILLIN

CASE	CLINICAL SUMMARY	STOOL CULTURE	TREATMENT	COURSE	WEIGHT
1. M.B. 2 mo.	Adm. 6/23/50 because of diarrhea for 10 days. Dehydrated, acidotic and afebrile on admission.	6/23 *Pr. vulgaris*	Procaine penicillin 150,000 U. I.M. daily 6/23 to 6/27. Sulfadiazine 0.3 Gm. q. 8 h. orally 6/23 to 6/27. Streptomycin 200,000 U. orally q. 6 h. 6/23 to 6/26.	Had fluids on 6/23. Normal stools by 6/26. Discharged 7/3.	6/23 7 lb. 6 oz. 6/30 7 lb. 13 oz.
2. R. B. 13 da.	Adm. 6/23/50 because of diarrhea for 3 days. Dehydrated and acidotic on adm. Afebrile. Had bilateral intercostal retractions and markedly dyspneic.	6/23 Negative	Procaine penicillin 150,000 U. I.M. daily 6/23 to 6/27. Sulfadiazine 0.15 Gm. q. 6 h. orally 6/23 to 6/27. Streptomycin 200,000 U. orally q. 6 h. 6/23 to 6/28. Neomycin 1,000 U. I.M. q. 6 h. 6/24 to 6/27.	Normal respirations by 6/25. Fed poorly and required fluids almost daily to 6/28. Normal stools by 7/3. Discharged 7/10.	6/23 4 lb. 14 oz. 7/21 6 lb.
3. D. B. 1 mo.	Adm. 6/26/50 because of diarrhea for 7 days. Dehydrated and afebrile on admission	6/28 Negative	Procaine penicillin 150,000 U. I.M. daily 6/26 to 7/3. Streptomycin 100,000 U. orally q. 6 h. 6/26 to 7/3.	Required blood and fluids 6/26 to 6/28. Normal stools by 7/3. Discharged 7/10.	6/26 6 lb. 4 oz. 7/5 7 lb. 2 oz.
4. D. C. 3 mo.	Adm. 6/29/50 because of diarrhea and vomiting for 3 days. Dehydrated with temp. of 104° F. on admission.	6/29 Negative	Procaine penicillin 150,000 U. I.M. daily 6/29 to 7/3. Sulfadiazine 0.3 Gm. q. 8 h. orally 6/29 to 7/1. Streptmycin 200,000 U. orally q. 6 h. 6/30 to 7/2.	Afebrile by 7/11. Sulfadiazine discontinued because of drug eruption 6/30. Normal stools by 7/1. Developed few liquid and semiliquid stools 7/7 and 7/8. Discharged 7/11.	6/29 12 lb. 7/11 11 lb. 12 oz.
5. S. M. 5 mo.	Adm. 6/23/50 because of burn of right wrist and diarrhea for 2 days. Had temp. of 101° F. and second degree infected burn right wrist.	6/27 *Pr. morganii*	Procaine penicillin 300,000 U. I.M. daily 6/23 to 6/28. Sulfadiazine 0.3 Gm. q. 6 h. orally 6/26 to 6/28.	Afebrile by 6/24. Developed nasopharyngitis and temp. of 102.4° F. 6/26. Afebrile 6/28. Normal stools 6/28. Released 6/28.	6/23 17 lb. 6/28 16 lb. 12 oz.

6. B. P. 10 mo.	Adm. 6/27/50 because of diarrhea for 8 days. Temp. of 101.6° F. and pharyngitis on admission.	6/27 *Pr. morganii*	Procaine penicillin 300,000 U. I.M. daily 6/27 to 7/3. Sulfadiazine 0.3 Gm. q. 6 h. orally 6/27 to 7/3. Streptomycin 200,000 U. q. 6 h. orally 6/28 to 7/3.	Required daily fluids 7/2. Had generalized convulsions on 6/28 which responded to sedation. Afebrile by 6/29. Normal stools 7/2. Discharged 7/6.	6/27 7/5	17 lb. 3 oz. 18 lb. 4 oz.	
7. A. P. 5 mo.	Adm. 6/9/50 because of a pneumonitis in right lower lung and diarrhea for 3 days which failed to respond to penicillin therapy. Temp. 101° F., respiration 60 on down.	6/14 Paracolon	Procaine penicillin 300,000 U. I.M. daily 6/9 to 6/22. Sulfadiazine 0.3 Gm. q. 6 h. orally 6/9 to 6/14, 6/18 to 6/22. Streptomycin 100,000 U. q. 6 h. orally 6/9 to 6/14.	Required fluids 6/9 and 6/14. Liquid and semiliquid stools persisted until 6/19. Discharged 6/23.	6/9 6/23	9 lb. 14 oz. 9 lb. 14 oz.	
8. W. T. 6 mo.	Adm. 6/24/50 because of diarrhea for 3 days. Temp. 101.4° F. Dehydrated. Nasopharyngitis present.	6/24 *Pr. morganii* 6/26 *Pr. morganii*	Procaine penicillin 300,000 U. I.M. daily 6/24 to 6/28, 7/14 to 7/19. Sulfadiazine 0.3 Gm. q. 6 h. orally 6/9 to 6/14, 6/18 to 6/22. Streptomycin 100,000 U. q. 6 h. orally 6/9 to 6/14.	Required fluids and blood 6/24. Required fluids 7/2 to 7/9. Soft green stools by 6/30. Developed liquid stools again on 7/1. Normal stools by 7/11. Discharged 7/22.	6/24 7/19	14 lb. 11 oz. 13 lb. 5 oz.	
9. R. W. 2 wk.	Adm. 6/9/50 because of diarrhea and fever for 1 day. Temp. 103.4° F. Pharyngitis present.	6/10 Paracolon 6/12 Negative	Procaine penicillin 150,000 U. I.M. daily 6/9 to 6/14. Sulfadiazine 0.1 Gm. q. 4 h. orally 6/9 to 6/12. Streptomycin 100,000 U. q. 6 h. orally 6/9 to 6/11.	Afebrile by 6/10. Normal stools 6/12. Discharged 6/16.	6/9 6/16	7 lb. 1 oz. 8 lb. 5 oz.	

found that 41.3 per cent of their cases of infantile diarrhea harbored Protei, Paracolobactra and *Ps. aeruginosa*. Other authors[14, 15, 16] have found *Ps. aeruginosa* in outbreaks of infantile diarrhea. There is a trend in public health laboratories[17] to recognize these bacteria as incitants in diarrheic disorders. One may suppose that cases of infantile diarrhea may be due to these microorganisms. In this study, however, *Ps. aeruginosa* was cultured from five patients and *Pr. morganii* from two after successful treatment and when the infants were already asymptomatic, whereas before therapy the stool cultures did not reveal these organisms. Thus we have to be cautious in the evaluation of the role of Protei, Paracolobactra and Pseudomonades in the present series.

There have been numerous reports on the use of sulfonamides in the treatment of specific and nonspecific diarrheas of infants.[18, 19] Sulfadiazine appears to be preferred to the other sulfonamides.

The use of oral streptomycin in diarrheal disorders[20] appeared to be beneficial. Seligman and associates[21] found, however, that this antibiotic is merely bacteriostatic. Stable and Philpott[22] stated that intramuscularly administered streptomycin appeared to control the Salmonella bacteremia in their patients but had no effect on the enterocolitis.

We observed a recurrence of the diarrhea in eight infants in our series, four to seven days after the sulfadiazine and streptomycin treatment was discontinued, which necessitated the institution of therapy with a different drug.

In the doses given by us, no blood levels were obtained in the examined cases one to four hours after the ingestion of Neobacin. Thus, renal damage through the excretion of neomycin or bacitracin did not have to be feared.

Neobacin was well tolerated. The tablets were crushed and given with applesauce or jelly. None of the infants who received it per os developed vomiting. No other side effects were observed. Neobacin was also easily combined with the routine antidiarrheic dietary regimen.

The average duration of diarrhea in infants treated with Neobacin (including those treated with Neobacin and procaine penicillin) was 3.34 days, as compared with 6.44 days in the control group. After Neobacin treatment, moreover, no recurrences were observed. Nine patients had unusual weight gains during treatment in spite of low calorie intake.

Stool counts on patients receiving Neobacin showed a marked depression of both the gram-positive and gram-negative intestinal flora.[23] One may expect Neobacin to be of value in infantile diarrhea because of this effect.

It is difficult to evaluate treatment of diarrheic disorders because of the seasonal variation of bacterial strains and the variability of their response to specific drug therapy.

It is believed that antibiotic therapy does play an important part in the treatment of diarrhea but we feel that the early administration of fluids and electrolytes is of paramount importance. The role of antibiotics is to depress the intestinal flora and fauna and to shorten the duration of diarrhea, so that further disturbances of the electrolyte balance cannot take place.

SUMMARY

A study of fifty-three patients with infantile diarrhea was carried out in order to determine the effectiveness of a combination of neomycin and bacitracin, called Neobacin, as compared with a control group treated with sulfadiazine, streptomycin, and penicillin alone or in combinations. All infants received the same general supportive and dietary therapy.

The Neobacin-treated group of infants showed a significant reduction in the duration of diarrhea, as compared with the control group. In addition, no recurrence of the diarrhea was observed in the patients receiving Neobacin.

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SINOBRONCHITIS IN INFANTS AND CHILDREN

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CLASSIC descriptions of sinus disease in children fail to recognize the frequent association of sinusitis and lower respiratory tract infection. More recently it has been hypothesized that sinobronchitis is seen far more commonly among infants and children with symptoms of chronic respiratory tract infection than among those presenting no respiratory symptomatology. In the following paragraphs is described a method for establishing the prevalence of sinobronchitis in several groups of pediatric patients. A discussion of the sinopulmonary lesions characterizing childhood sinobronchial disease is presented, together with a summation of the pathogenesis of the infection. Modifying somewhat the terms of Dutton and Fuchlow,[1] sinobronchitis is here defined as "involvement of the sinus membranes by an infectious process of sufficient intensity to have implanted itself likewise upon the bronchial mucosa either *directly* (by means of contiguous extension or postnasal secretion) or *indirectly* (by lymphatic spread)."

MATERIAL AND METHODS

Group Selection.—Three hundred eighty-four patient records of admissions to the medical service of Children's Hospital of Pittsburgh between Sept. 1, 1946, and Sept. 1, 1949, were selected for review and divided into three groups as follows:

Group 1: From files of the Department of Radiology were obtained the case numbers of all pediatric patients hospitalized from September, 1946, through June, 1949, on whom there were reported sinus and pulmonary roentgenograms. The case records of 312 children so identified were next examined, and clinical and laboratory findings of all who had presented symptoms associated with chronic upper or lower respiratory tract infection were reviewed for this study. The group so designated consists of 275 patients admitted during thirty-four consecutive months with complaints of chronic respiratory tract infection that prompted roentgen examination of chests and sinuses.

Group 2: Twenty-nine children admitted during July, 1949, were carefully selected for sinopulmonary roentgen examination because their presenting symptomatology of chronic respiratory infection was analagous to the complaints of patients comprising Group 1.

Group 3: During August, 1949, an attempt was made to evaluate roentgenographically the sinopulmonary status of every medical admission over 16 months of age. Of a total of 117 patient admissions only patients severely incapacitated (i.e., suffering from acute or chronic neurologic or cardiac illnesses), patients who were moribund, or patients hospitalized for less than forty-eight hours were omitted from this roentgenogram survey. Eighty patients were thus examined, and from among these twenty-seven patients were separated whose clinical records included symptoms of chronic respiratory tract infection. An additional twenty-six

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patients with no symptoms of respiratory tract involvement were selected from the series to serve as a control section.

Group Variability.—Although chronic sinobronchial disease symptomatology was intended as the basis of selection of patients in Group 1, it seemed possible that other clinical factors had prompted roentgen examination of these patients and thus the validity of group sampling was open to question. However, when patients with identical symptomatology were selected in Group 2 from among 114 medical admissions in July, 1949, the prevalence of sinobronchitis was almost identical with figures for Group 1, probably indicating that variables caused no significant disproportion in selection of Group 1 children.

Since patients of both Groups 1 and 2 had been selected first on the basis of their presenting symptoms, and later clinically evaluated, it was also desirable to determine whether such an approach would compare favorably with a series of patients studied roentgenographically first, and then classified clinically. The Group 3 survey made in August, 1949, embodied this approach in a patient series, and again the prevalence of sinobronchitis corresponded to that in Groups 1 and 2.

Disease Classification.—Of 384 patients examined, 126 children showed roentgen evidence of sinobronchial disease. Three classifications of degree of respiratory tract involvement based upon these studies were established. The first class, designated as *slight,* showed minimal thickening of the sinus membrane with faint overall changes in sinus density, associated with prominent hilar nodes or faint increases in pulmonary markings. The second class, designated as *moderate,* showed on roentgen examination definite membrane swelling and sinus opacity, together with accentuation of bronchovesicular markings. The third class, designated as *advanced,* showed unequivocal opacity of the sinuses (in some cases there were also demonstrable cystic or polypoid changes) together with bronchopneumonic infiltrations or lobar consolidation.[2, 3]

TABLE I. INCIDENCE OF SINOBRONCHITIS

GROUP	DEFINITION	TOTAL	POSITIVE SINO-BRONCHITIS	NEGATIVE SINO-BRONCHITIS	PER CENT SINO-BRONCHITIS
1	Chronic respiratory infection (Sept. 1, 1946, to July 1, 1949)	276	105	170	38.1
2	Chronic respiratory infection (July, 1949)	29	11	18	37.9
3	Chronic respiratory infection (August, 1949)	27	10	17	37.0
	No respiratory infection (August, 1949)	26	2	24	7.7

RESULTS

Prevalence.—The prevalence of sinobronchitis in the three groups is enumerated in Table I. The prevalence of roentgeno-positive sinobronchial disease among infants and children in the control group was 7.7 per cent. Among patients hospitalized with symptoms of chronic respiratory infection, the prevalence of sinobronchitis in Groups 1, 2, and 3 approx-

imated 38 per cent. It is evident from these figures that sinobronchial infection occurs with five times the frequency in children suffering from chronic respiratory disease as compared with children hospitalized with nonrespiratory illnesses.

Estimates of the prevalence of sinobronchitis in childhood have not been previously recorded. Among adult patients, Kistner[4] found sinusitis complicating 97 per cent of 196 consecutive cases of bronchitis, while Dunham and Skavlem[5] reported coexistent sinusitis in 73 per cent of twenty-six cases of bronchial infection in young adults.

tients, with distribution by age constant for each group. From Table III it is evident that childhood sinobronchitis has no apparent sex predilection as the ratio of male to female patients corresponds to that of total hospital admissions (five males: four females).

To discern any effect of seasonal variations upon sinobronchial disease, the entire series was broken down into monthly units whose distribution proved to be relatively constant in the thirty-four-month survey period.

Degree of Infection.—Table IV records the age and degree of sinobronchial involvement among the patients

TABLE II. AGE AND PREVALENCE OF SINOBRONCHITIS (CONTROL GROUP OMITTED)

AGE (YEARS)	TOTAL PATIENTS	CASES OF SINOBRONCHITIS	PER CENT OF SINOBRONCHITIS
Under 3	46	19	41.3
3-5	76	43	56.6
6-8	106	46	43.4
9-11	59	12	20.3
12-15	44	6	13.6
Totals	331	126	Average 38.1

TABLE III. SEX AND PREVALENCE OF SINOBRONCHITIS (CONTROL GROUP OMITTED)

SEX	TOTAL	CASES OF SINOBRONCHITIS	PER CENT OF SINOBRONCHITIS
Male	198	74	37.4
Female	133	52	39.1
Totals	331	126	Average 38.3

Group Control.—Each group was broken down individually to demonstrate that there was no disproportion in age or sex distribution which might cause a discrepancy in the calculation of the prevalence of sinobronchial disease within the several groups. Tables II and III summarize the frequency of occurrence of infection by age and sex in all patients except the control section. Table II clearly illustrates the increased prevalence of sinobronchitis in the younger patients with positive sinus and pulmonary roentgenograms. About one-sixth of these patients were under 3 years and one-half were 5 years of age or under; only one-sixth were included in the age group of 9 to 15 years. From this table the prevalence of more advanced sinobronchial disease among the younger children (i.e., under 9 years of age) is apparent. A careful analysis of patient records does not afford an acceptable explanation for this trend.

Extent and Site of Pulmonary Involvement.—A more detailed tabulation of the pulmonary pathology present in 126 children is presented in Table V. It is here evident that bilateral pulmonary involvement was a most consistent roentgen pattern (43 per cent of patients) and right-sided bronchopneumonitis occurred more often than left. Areas of pulmonary consolidation were present in varying extent in approximately 21 per cent of patients, while emphysema, empyema, or pleural thickening was reported infrequently.

Our experience would confirm the postulate that the most significant and reliable manifestation of pulmonary disease is the roentgen demonstration of bilateral increase in width and density of the hila with accentuation of the perivascular and peribronchial markings in these areas.[6, 7] Prominence of the hilar shadows or slight thickening of the bronchovesicular markings present in early cases represent the mild beginnings of the pervasive chronic disease. Gradually there occurs a progressive accentuation of trunk markings which is most evident at the lung bases in older children (5 to 9 years). These changes may represent a frequently associated peribronchial pneumonitis. Only in the most advanced cases is there diffuse parenchymal involve-

TABLE IV. AGE AND EXTENT OF SINOBRONCHITIS (CONTROL GROUP OMITTED)

SINOBRONCHITIS	NO. PATIENTS	AGE IN YEARS: UNDER 3 NO.	UNDER 3 %	3-5 NO.	3-5 %	6-8 NO.	6-8 %	9-11 NO.	9-11 %	12-15 NO.	12-15 %
Slight	30	2	11.1	8	18.7	12	26.1	6	46.2	2	33.3
Moderate	43	6	33.3	18	41.8	15	32.6	2	15.3	2	33.3
Advanced	53	10	55.6	17	39.5	19	41.3	5	38.5	2	33.3
Totals	126	18	100.0	43	100.0	46	100.0	13	100.0	6	100.0

TABLE V. EXTENT AND SITE OF PULMONARY INVOLVEMENT (126 CASES)

	CLASSIFICATION: NO PULMONARY PATHOLOGY	SLIGHT	MODERATE	ADVANCED	ADENOPATHY	PULMONARY PATHOLOGY: BRONCHIAL THICKENING	INFILTRATION: LIMITED	INFILTRATION: DIFFUSE	INFILTRATION: CONSOLIDATION	EMPHYSEMA	EFFUSION	PLEURAL THICKENING	ATELECTASIS	BRONCHIECTASIS
Right lung		5	12	18									1	
Upper lobe							1	2	1					
Middle lobe						1		1	3		1	1		
Lower lobe						16	5	1	9	2	2	2		1
Hilar					8	5	2		3					
Left lung		2	4	12										
Upper lobe							3	8	1	1				
Lower lobe						1		3	2	1	1	1	1	
Hilar					2	2	3		1					
Bilateral		23	27	23										
Upper lobes						3	2	1						
Lower lobes						23	4	2	1	5				4
Hilar					46	28	2	2	3					
Totals	99	30	43	53										

TABLE VI. ETIOLOGY AND COMPLICATIONS OF SINOBRONCHITIS (126 CASES)

ETIOLOGY	TOTALS	
Upper respiratory tract infection	84	
Tonsillopharyngitis		41
"Grippe"		28
Acute otitis media		15
Acute infectious disease	21	
Pertussis		10
Rubeola		7
Parotitis		3
Scarlatina		1
Pneumonia (all types)	16	
COMPLICATIONS		
Local	19	
Cellulitis		12
Mastoiditis		7
Pulmonary	43	
Bronchopneumonia		19
Lobar pneumonia		11
Tracheobronchitis		8
Bronchiectasis		5
Allergic	47	
Asthmatic bronchitis		26
Hay fever		8
Rhinitis		7
Eczema		4
Angioneurotic edema		2
Miscellaneous	8	
Rheumatic fever		4
Chorea		1
Erythema multiforme		1
Meningitis (pneumococcic)		1
Purpura		1

ment described by the roentgenologist as scattered areas resembling minute bronchopneumonic infiltrations.[8]

Etiology, Complications, and Symptoms.—In slightly less than one-half of the 126 children with sinobronchitis the first symptoms of sinobronchial disease had developed secondarily to an acute upper or lower respiratory tract infection. The most frequent complications noted in this series were allergic disorders and pulmonary infections, which were present singly or in combination in 46 per cent of patients. Table VI also lists the complaints which were recorded at the time of the patient's hospitalization and tabulates as well the duration of symptoms which were associated clinically with the individual's sinobronchitis.

In Table VII we noted that the complaints most commonly reiterated were recurrent head colds and chronic coughs. Next in order of frequency were expectoration, low-grade fever, and rhinorrhea. In a study just published separately we have noted that children with an allergic diathesis seem, significantly, to be included among those patients most often presenting chronic complaints; their symptoms usually include asthmatic distress evidenced by tight coughing or wheezing.[9, 10]

DISCUSSION

The concept of sinobronchitis as a clinical entity has evolved from studies correlating the pathologic physiology of upper and lower respiratory tracts, modified by consideration of the role chronic sinusitis plays in perpetuation of respiratory disease. As early as 1926, Mullin and Ryder[11] concluded from a ten-year study of sinus-chest infections in children that "bronchitis clears unless fed and fostered by chronic sinus infection." The radiologists Wasson and Waltz[12] further corroborated the hypothesis that primary sinus infection spreads to involve the bronchi secondarily, while Farrell[13] noted that in 80 per cent of adult patients suffering from bronchiectasis symptoms of sinobronchial infection had been manifest within the first decade of life.

Acute sinobronchitis arises from bacterial infection of the respiratory tract epithelium; the inflammation spreads rapidly by direct extension to involve the mucosa of contiguous sinus and bronchial passages.[14] The all-inclusive term "sinobronchitis" as used commonly refers more specifi-

TABLE VII. PRESENTING COMPLAINTS; DURATION OF SYMPTOMS (126 CASES)

	WEEKS		MONTHS					YEARS			TOTAL
	2	3	1	2	3	6	12	1-2	3-4	5 OR MORE	
Recurrent head colds	9	12	17	17	5	10	15	8	2	1	96
Cough	5	4	11	8	15	19	10	6	8	4	90
Expectoration	16	4	9	4	5	13	4	3	2	1	61
Low-grade fever	10	11	8	6	7	2	3	2	1	2	52
Rhinorrhea	8	2	—	4	11	2	2	1	4	—	34
Headache	—	5	3	4	6	4	3	4	—	3	32
Postnasal drip	1	—	—	4	3	8	5	7	—	1	29
Weight loss	1	—	2	1	3	9	4	2	3	3	28
Asthma or wheezing	2	4	—	—	1	2	4	4	3	2	22
Sore throat	5	2	—	1	—	1	—	—	—	—	9
Swelling (eye, forehead, face)	4	2	2	—	—	—	—	—	—	—	8
Choking or vomiting	2	3	1	—	1	—	—	—	—	—	
Snoring, hoarseness	2	2	3	2	—	—	—	—	—	—	9
Foul breath	—	—	—	1	—	—	2	—	1	—	4

cally to three pathologic stages of sinobronchial infection:

Stage 1: The initial infectious (bacterial) involvement of the mucosa. In this stage the pathologist describes acute inflammatory changes in the soft red membrane whose swelling may occlude the orifice of a sinus or diminish the lumen of a bronchus. There is an excessive secretion of thin mucous exudate which soon becomes purulent and tenacious, producing empyema of the sinuses and an incipient tracheitis, characterized clinically by a dry, spasmodic cough.

Stage 2: The stage of hyperplastic (allergic) reaction, wherein the edematous nonpurulent membrane may swell from one-eighth to one-fourth inch in thickness (normal: one-thirty-second of an inch). Desquamation of the cilia, edema of the tunica propria with glandular and connective tissue proliferation, and mucosal infiltration with large numbers of eosinophilic cells are evident microscopically. Clinically, the cough has become more prolonged, and bronchorrhea perpetuates the infectious cycle.

Stage 3: The stage of chronic suppurative (or mixed) sinobronchitis. Boggy pale mucous membranes of the respiratory tract appear diffusely thickened, while the tissue is edematous and infiltrated with leucocytic cells. There is an elaborate proliferation of connective tissue, frequently associated with polypoid hyperplasia. The sinuses are often completely filled with a foul-smelling purulent debris, while in the pulmonary tract a bronchiolitic reaction progresses toward the more advanced stage of bronchiectasis. The patient complains of irrepressible coughing productive of quantities of foul tenacious sputum.

These stages represent the progressive pathology of the childhood disease entity of sinobronchitis which we noted so frequently complicating respiratory tract infection of hospitalized pediatric patients.

SUMMARY AND CONCLUSIONS

The medical records of 384 children hospitalized during a three-year period who presented complaints of chronic respiratory tract infection were analyzed with regard to (a) prevalence of sinobronchitis, (b) variation of sinobronchitis by age groups, (c) the sinopulmonary roentgenographic changes most consistently noted, and (d) the etiology, symptoms, and com-

plications of sinobronchial disease most frequently encountered. Progressive stages in the pathologic physiology of the disease were discussed, and the following observations were made:

1. The prevalence of sinobronchitis in a control group of children presenting no symptoms of respiratory tract infection was 7.7 per cent.

2. The prevalence of demonstrable sinobronchitis in pediatric patients with symptoms attributable to chronic respiratory tract infection averaged 37.7 per cent.

3. The prevalence of sinobronchial infection was greatest in children under 9 years of age (46.8 per cent), and moderate to advanced sinobronchitis was present more often in children 5 years of age or under.

The author is indebted to Dr. S. S. Stevenson, Research Professor of Pediatrics in the School of Medicine, and to Dr. P. A. Densen, Associate Professor of Biostatistics in the School of Public Health, the University of Pittsburgh, for guidance in correlation of statistical method and clinical observation.

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A TREATMENT PROGRAM FOR CHRONIC CHILDHOOD SINOBRONCHITIS

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THE prevalence of sinobronchial disease in a selected group of medical patients admitted to the Children's Hospital of Pittsburgh has been reviewed.[1] In this paper are presented in some detail clinical experiences with various medications administered in several combinations in an attempt to formulate a more satisfactory regimen for treatment of chronic upper and lower respiratory tract infections in children.

THERAPEUTIC PROGRAM

A treatment program was conceived and instituted for the empirical management of fifty-four consecutive pediatric admissions to Children's Hospital requiring therapy for chronic sinobronchitis. Although these cases represent only a small series, the studies were well controlled, and preliminary evaluations based upon observations of serial sinus roentgenograms taken before, during, and after treatment were encouraging. The patients may be separated on a basis of therapeutic regimen into three major groups as follows:

Group 1 was composed of sixteen patients whose sinobronchial infection was evident roentgenographically. In eleven children additional complications were noted. Therapy consisted of an antihistaminic drug* administered orally to all patients, together with parenteral penicillin, the dosage, frequency, and amount of medication varying as detailed in Table I.

Group 2 consisted of eighteen patients similarly selected and treated, the single modification of therapy being the addition of aerosol penicillin inhalations. This regimen is outlined in Table II.

Group 3 included twenty patients whose treatment paralleled that described for the above group with the addition of Paredrine-penicillin† nose drops to the therapeutic program. These cases are summarized in Table III.

In a group of eight patients, treatment with parenteral penicillin alone provided such a uniformly poor response that the regimen has not been included here.

DISCUSSION

The results of the combination of therapy employed in the treatment of Group 3 patients were uniformly better than either of the other programs, as is shown in Table IV. A single daily intramuscular injection of procaine penicillin evoked as satisfactory a clinical response as more intensive crystalline penicillin administration. The antihistaminic syrup was readily acceptable to the children and well tolerated. Intranasal administration of

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*Syrup of Histadyl, Eli Lilly and Company, Indianapolis.

†Par-pen, Smith, Kline and French Laboratories, Philadelphia.

TABLE I. PARENTERAL PENICILLIN WITH ANTIHISTAMINIC (GROUP 1)

CASE NO.	AGE (YR.)	COMPLICATIONS	DAYS OF THERAPY	INTRAMUSCULAR PENICILLIN DOSAGE/DAY	ANTIHISTAMINIC DRUG DOSAGE/DAY	IMPROVEMENT (X-RAY)
1	14	None	7	75,000 U. q. 3 hr.	20 mg. t.i.d.	None
2	6	None	5	50,000 U. q. 3 hr.	20 mg. t.i.d.	Good
3	7	None	5	50,000 U. q. 3 hr.	20 mg. t.i.d.	Fair
4	6	Acute tonsillitis	5	50,000 U. q. 3 hr.	20 mg. q.i.d.	None
5	6	Acute ethmoiditis	6	50,000 U. q. 3 hr.	20 mg. 6 × daily	None
6	11	Bronchopneumonia	5	100,000 U. q. 4 hr.	50 mg. t.i.d.	Good
7	9	Lobar pneumonia	6	50,000 U. q. 3 hr.	20 mg. q.i.d.	Fair
8	4	Tracheobronchitis	5	50,000 U. q. 3 hr.	20 mg. q.i.d.	None
9	4	Bronchial asthma	6	75,000 U. q. 3 hr.	20 mg. t.i.d.	Fair
10	8	Bronchiectasis	9	75,000 U. q. 3 hr.	30 mg. t.i.d.	Good
11	8	None	8	300,000 U. procaine	30 mg. t.i.d.	None
12	5	None	5	300,000 U. procaine	20 mg. t.i.d.	None
13	2	Lobar pneumonia	10	300,000 U. procaine	20 mg. q.i.d.	Fair
14	3	Chronic bronchitis	6	300,000 U. procaine	20 mg. q.i.d.	None
15	1½	Bronchial asthma	7	300,000 U. procaine	20 mg. t.i.d.	None
16	10	Bronchiectasis	14	300,000 U. procaine	30 mg. q.i.d.	None

TABLE II. PARENTERAL AND AEROSOL PENICILLIN WITH ANTIHISTAMINIC (GROUP 2)

CASE NO.	AGE (YR.)	COMPLICATIONS	DAYS OF THERAPY	I.M. PENICILLIN DOSAGE/DAY Q. 3 HR.	AEROSOL PENICILLIN DOSAGE/DAY	ANTIHISTAMINIC DRUG DOSAGE/DAY	IMPROVEMENT (X-RAY)
1	5½	None	5	75,000 U.	50,000 U. q. 3 hr.	50 mg. t.i.d.	Excellent
2	9	None	9	75,000 U.	100,000 U. 7 × daily	30 mg. q.i.d.	Good
3	3	None	9	75,000 U.	75,000 U. q.i.d.	15 mg. q.i.d.	Fair
4	7	Acute sinusitis	15	30,000 U.	50,000 U. q.i.d.	15 mg. t.i.d.	Good
5	3	Acute otitis media	5	100,000 U.	50,000 U. q.i.d.	20 mg. t.i.d.	Excellent
6	14	Allergic rhinitis	6	30,000 U.	10,000 U. q. 3 hr.	50 mg. t.i.d.	Excellent
7	6	Bronchopneumonia	9	20,000 U.	50,000 U. q.i.d.	50 mg. t.i.d.	Good
8	7	Bronchopneumonia	13	30,000 U.	100,000 U. q.i.d.	25 mg. t.i.d.	Good
9	5	Bronchial asthma	8	30,000 U.	10,000 U. q. 3 hr.	50 mg. t.i.d.	Good
10	6	Chronic bronchitis	10	25,000 U.	25,000 U. q.i.d.	30 mg. q.i.d.	Good
11	10	Chronic bronchitis	10	50,000 U.	30,000 U. q.i.d.	50 mg. t.i.d.	Excellent
12	5	Chronic bronchitis	8	30,000 U.	30,000 U. t.i.d.	15 mg. t.i.d.	Excellent
13	9	None	6	300,000 U. procaine	50,000 U. t.i.d.	50 mg. q.i.d.	Fair
14	4	Acute tonsillitis	5	300,000 U. procaine	20,000 U. q.i.d.	30 mg. q.i.d.	Good
15	4	Bronchopneumonia	6	300,000 U. procaine	100,000 U. q.i.d.	30 mg. q.i.d.	Fair
16	4	Bronchial asthma	7	300,000 U. procaine	75,000 U. q.i.d.	45 mg. q.i.d.	None
17	2	Bronchial asthma	11	300,000 U. procaine	30,000 U. t.i.d.	20 mg. q.i.d.	None
18	12	Pyelitis	5	300,000 U. procaine	100,000 U. q.i.d.	50 mg. q.i.d.	Fair

TABLE III. PARENTERAL AND AEROSOL PENICILLIN, ANTIHISTAMINIC DRUG, PENICILLIN-PAREDRINE NOSE DROPS (GROUP 3)

CASE NO.	AGE (YR.)	COMPLICATIONS	DAYS OF THERAPY	I.M. PENICILLIN DOSAGE/DAY	AEROSOL PENICILLIN DOSAGE Q.I.D.	ANTIHISTAMINIC DRUG DOSAGE Q.I.D.	NOSE DROPS GIVEN	IMPROVEMENT (X-RAY)
1	3	None	6	50,000 U. q. 3 hr.	50,000 U.	15 mg.	q.i.d.	Excellent
2	6	None	5	75,000 U. q. 4 hr.	50,000 U.	30 mg.	q.i.d.	Excellent
3	5	Acute tonsillitis	4	50,000 U. q. 3 hr.	50,000 U.	30 mg.	t.i.d.	Good
4	1½	Bronchopneumonia	8	75,000 U. q. 3 hr.	75,000 U.	20 mg.	q.i.d.	Excellent
5	2	Bronchial asthma	5	75,000 U. q. 3 hr.	75,000 U.	20 mg.	q.i.d.	Excellent
6	11	Meningitis (pneu.)	7	100,000 U. q. 4 hr.	100,000 U.	30 mg.	q.i.d.	Excellent
7	5	None	5	300,000 U. procaine	75,000 U.	30 mg.	q.i.d.	Excellent
8	8	None	5	300,000 U. procaine	100,000 U.	30 mg.	q.i.d.	Excellent
9	3½	None	4	300,000 U. procaine	100,000 U.	30 mg.	q.i.d.	None
10	4	None	7	300,000 U. procaine	75,000 U.	20 mg.	q.i.d.	Fair
11	7	None	5	300,000 U. procaine	75,000 U.	30 mg.	q.i.d.	Good
12	7	None	5	300,000 U. procaine	100,000 U.	30 mg.	q.i.d.	Good
13	8	Acute ethmoiditis	5	300,000 U. procaine	100,000 U.	30 mg.	t.i.d.	Good
14	13	Acute ethmoiditis	5	300,000 U. procaine	100,000 U.	50 mg.	t.i.d.	Excellent
15	6	Bronchopneumonia	5	300,000 U. procaine	75,000 U.	30 mg.	q.i.d.	Excellent
16	3	Tracheobronchitis	8	300,000 U. procaine	75,000 U.	15 mg.	q.i.d.	Excellent
17	7	Bronchial asthma	6	300,000 U. procaine	75,000 U.	30 mg.	q.i.d.	Good
18	10	Bronchial asthma	9	300,000 U. procaine	100,000 U.	30 mg.	q.i.d.	Excellent
19	7	Chronic bronchitis	14	300,000 U. procaine	75,000 U.	20 mg.	q.i.d.	Excellent
20	15	Bronchiectasis	21	300,000 U. procaine	100,000 U.	50 mg.	t.i.d.	Excellent

aerosol penicillin, when immediately preceded by nasal instillation of a Paredrine-penicillin solution, proved most efficacious in inhibiting the inflammatory processes within the respiratory tract. The systematized therapeutic regimen is the most satisfactory method for treatment of chronic sinobronchial infection yet undertaken by us.

TABLE IV

GROUP	TOTAL PATIENTS TREATED	RESPONSE TO THERAPY							
		NONE		FAIR		GOOD		EXCELLENT	
		NO.	%	NO.	%	NO.	%	NO.	%
1	16	9	56	4	25	3	19	–	–
2	18	2	11	4	22	7	39	5	28
3	20	1	5	1	5	5	25	13	65

Evaluation of response to therapy was based upon changes noted in roentgenograms made on completion of a treatment program in comparison with studies made prior to initiation of therapy. Improvement was classified "none" when no difference was noted or when the sinuses seemed more congested at the conclusion of the course of therapy. A "fair" response was recorded when membrane shrinkage and/or decreased sinus opacity was evident. A "good" response was recorded when complete clearing of opacity on the diseased sinuses had occurred. An "excellent" classification was accorded only when both the sinus opacity had disappeared and membrane swelling was notably diminished.

During the courses of therapy administered to Groups 1 and 2, experience dictated several noteworthy modifications of technique. First, unsatisfactory results occurred consistently in those children to whom the aerosol penicillin was administered by oral inhalations, thus demonstrating that chronic purulent sinusitis responds only to intranasal aerosol inhalation, posing a problem of therapy in infants. Second, in numerous patients in whom hyperplastic nasal mucosa obstructed the ostia of the sinuses, neither intranasal aerosol nor intensive concentrations of parenterally administered penicillin were able to effect clearing of the pus-filled sinuses. Consequently, in the third patient group it was found that a Paredrine-penicillin solution, instilled into the child's nostrils just prior to aerosol inhalations, effected shrinkage of the swollen membrane and permitted drainage of intrasinal matter, thus allowing penetration of the vaporized antibiotic into the sinus cavity. Third, one of our associates contrived, in treating children under 3 years of age, a method of administering aerosol penicillin by attaching a standard plastic nebulizer to a porthole penetrating the headboard of a transparent Plexiglas tent so constructed as to enclose completely the infant's head and neck.[2]

Diverse approaches to therapy have been advocated for the treatment of chronic sinobronchial infection. Several that have received close clinical scrutiny include: (1) irradiation of the sinuses and hilar areas of the lungs,[3, 4] (2) local measures, including intranasal ephedrine with sulfonamides[5] or penicillin in suspension, (3) systemic measures, either antibiotic or chemotherapeutic, (4) sinus surgery, said to eliminate foci of in-

fection and permit free drainage of the sinuses,[6] and (5) combined measures, employing several of the abovementioned techniques. For varying periods each of these regimens, with the single exception of surgical intervention, has previously been evaluated in our clinic; none has given satisfactory results.

Hansel in 1941 foresaw that antibiotic therapy could not alone prevent the inevitable exacerbations of chronic sinusitis, reasoning that "only when antibiotic therapy can be supplemented with additional anti-allergic measures will treatment of sinus disease be successful."[8] The antihistaminic drugs, first introduced in 1946, appear as logical adjuvants to antibiotics in treatment of chronic respiratory tract disease. In such combination is embodied the pharmacologic rationale of eliminating the infectious process while simultaneously controlling the allergic response of the sinobronchial mucosa to bacterial protein. Thus the vicious cycle of infection-reaction is interrupted and in time the hyperplasia of the membrane regresses, permitting normal epithelium to regenerate. Moreover, such changes in the membrane lining the paranasal sinuses and bronchial tree can be demonstrated on serial roentgen studies of patients whose chronic sinobronchitis is responsive to such combined therapy.

SUMMARY

In the evolution of a program for treatment of chronic sinobronchial infection, preliminary studies of fifty-four pediatric patients disclosed a most satisfactory clinical response to parenteral and intranasal penicillin when administered in conjunction with Paredrine-penicillin nose drops and antihistaminic medication.

The authors are indebted to the Medical and Nursing Staffs of Children's Hospital for their encouragement and cooperation in establishing these controlled therapeutic programs. The advice and assistance of the late Anna Marie Schaper, Chief Technician of the Department of Radiology, were greatly appreciated. Dr. Jane Worcester of the Department of Biostatistics of the Harvard Graduate School of Public Health kindly corroborated the significance of the data contained in Table IV.

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CLINICAL EVALUATION OF STREPTOMYCIN IN THE TREATMENT OF BACILLARY DYSENTERY IN INFANCY AND CHILDHOOD

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BACILLARY dysentery is a serious disease easily contracted in infancy and childhood, being most prevalent in summer and autumn. In the past the mortality rate was high, up to 35.8 per cent according to Ouyang's report,[1] but has been very much reduced since the introduction of sulfonamides.[2, 3, 4] The advancement of fluid therapy and the discovery of streptomycin in the past few years have resulted in more favorable results in the treatment of bacillary dysentery among children.

SUBJECTS AND METHOD

This report is limited to children suffering from bacillary dysentery with positive stool cultures. In the period from January, 1949, to June, 1950, 244 clinically diagnosed cases of bacillary dysentery were admitted to this hospital; 130 patients had positive stool cultures of Shigella group and are included in the present study. Patients with only clinical symptoms and signs, even definite dysenteric stools, but with negative stool cultures, were excluded. Most of them were admitted in summer and autumn. One hundred ten cases occurred in children from 1 to 5 years of age, twenty cases in those under 1 and over 5 years of age; seventy-five were in males and fifty-five in females. Treatment was divided into four groups: Group 1, streptomycin Group A; Group 2, streptomycin Group B (after failure of sulfonamides); Group 3, combined therapy group; and Group 4, control group (sulfonamides alone).

Causative Organisms.—Most of the cases, 122 (93.8 per cent), belong to the Shigella Flexner type, among which 120 cases were Flexner type II (Boyd's type II), in two cases the strain being unidentified; three cases of *Shigella shigae;* four cases of *Shigella ambigua,* and one case of *Shigella sonnei* (Table I). In one case the first stool culture revealed Flexner type II, but the second stool culture showed *S. sonnei*; this case was thought to have a mixed infection.

Condition of Illness.—Most of the patients were admitted within two weeks after the onset of illness and were defined as early cases. Those of more than two weeks' duration were defined as late cases (Table II). The severity of disease was classified into three groups; namely, severe, moderate, and mild. The severe cases usually had symptoms of convulsion, delirium, marked dehydration (body weight usually reduced 10 per cent), acidosis with 6 to 24 per cent CO_2 combining power, body temperature of more than 40° C., and frequency of bowel movements more than twenty

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Read before the Third Convention of The Chinese Pediatric Society, Peking, Aug. 25, 1950.

times daily. Moderate cases had moderate dehydration, acidosis, body temperature being around 40° C., and bowel movements about twenty times daily. More than half of our cases (85 cases) belong to the severe group. Among the early cases the duration of illness varied from two hours to fourteen days with an average of two to three days; as for the late cases the duration varied from fifteen to thirty days with an average of more than twenty days.

to 80 mg. per kilogram of body weight per day divided into six doses orally, and 40 mg. per kilogram of body weight per day divided into two, four, or six doses intramuscularly. The treatment was discontinued after three days of normal stools. In Group 4, the dosage of sulfonamides was 0.2 Gm. per kilogram of body weight the first day, followed by 0.1 to 0.15 Gm. per kilogram of body weight daily in six divided doses orally or parenterally.

TABLE I. CLASSIFICATION OF SHIGELLA ORGANISMS

GROUPS	S. SHIGAE	FLEXNER		S. AMBIGUA	S. SONNEI	TOTAL
		FLEXNER TYPE II (BOYD'S TYPE II)	UNIDENTIFIED STRAIN			
Streptomycin A	0	34	1	0	1	36
Streptomycin B (after failure of sulfonamides)	2	29	0	0	0	31
Combined	1	28	0	0	0	29
Control	0	29	1	4	0	34
Total	3	122		4	1	130

TABLE II. CONDITION OF ILLNESS

GROUPS		SEVERE	MODERATE	MILD	TOTAL
Streptomycin A	Early case	22	7	6	35
	Late case	0	0	1	1
Streptomycin B (after failure of sulfonamides)	Early case	23	4	2	29
	Late case	1	0	1	2
Combined	Early case	18	4	5	27
	Late case	0	2	0	2
Control	Early case	20	7	3	30
	Late case	1	1	2	4
Total		85	25	20	130

Methods of Treatment.—

A. Streptomycin therapy: The patients in Groups 1, 2, and 3 were given streptomycin after admission. The patients in Group 2 received streptomycin three to ten days after failure of sulfonamides. The streptomycin was given both orally and intramuscularly. The dosage was 60

B. Fluid therapy: For all the patients with toxic manifestations, dehydration, and acidosis, fluid therapy was given (Table III). The amount of fluid given depended on the severity of disease and the degree of dehydration, but for the late cases the amount of fluid given in the first two days was reduced to one-half or less

TABLE III. FLUID THERAPY

THERAPY	SEVERITY		
	VERY SEVERE	MODERATE	MILD
Initial hydration	5-10% glucose 3 parts 0.85% saline 2 parts M/6 sod. lact. 1 part 20-40 c.c./kg. (by venoclysis 20-30 Gtt./min.)	5% glucose 3 parts 0.85% saline 2 parts M/6 sod. lact. 1 part 10-30 c.c./kg. (by venoclysis or hypodermolysis)	5% glucose 1 part 0.85% saline 1 part 10-30 c.c./kg. (by hypodermoclysis)
Treatment of shock	Blood transfusion 10-20 c.c./kg. (I.V.)	If indicated	
Correction of acidosis	Calculated amount of alkaline. (Best to give ½ or ⅔ of the calculated dose.) (1) 55-CO_2 content × 0.3 body wt. (kg.) = $\frac{\text{c.c. Molar Sod. Lactate}}{\text{(Hartmann)}}$ (2) 55-CO_2 content × body wt. (kg.) × 0.026 = $\frac{\text{(Gram of } NaHCO_3\text{}}{\text{(Nelson)}}$		
Maintenance of water, electrolytes, and nutrition	"3:2:1" solution or 5% glucose 120-250 c.c./kg. in 24 hours. Blood or plasma transfusions repeated. Vitamins B, C, and K.		
Oral feeding	Diet: *Infants:* Breast milk or diluted whole milk except in cases of vomiting. Milk dilution { 1:4 first day; 1:3, 1:2, 1:1 subsequent days } Skimmed milk or lactic acid milk (0.2-0.3%), if indicated. *Children:* Rice water or liquid diet (first 1-2 days), q.2.h. Amount increasing in a staircase manner until a basal requirement is reached. (50-80 calories/kg. in 24 hours.) H.C. semiliquid, soft or full diet (subsequent days). NaCl 0.5% solution, CHO 5% glucose water } as indicated Potassium mixture solution (10%) 5 c.c. t.i.d. or q.i.d. (Pot. acetate, pot. bicarbonate and pot. citrate) $NaHCO_3$ calculated amount. Orange juice and carrot juice given freely if possible. Apple purée if indicated.		
Remarks: CO_2 content Loss of body wt.	6-24 vol. % 10%	25-34 vol. % 6%	35-45 vol. % 3%

TABLE IV. SENSITIVITY TEST OF STREPTOMYCIN TO SHIGELLA ORGANISMS

GROUPS	DEGREE OF SENSITIVITY			AVERAGE MM. (%)
	15 MM.	10-15 MM.	10 MM.	
Streptomycin A	10	15	0	14.32
Streptomycin B (after failure of sulfonamides)	6	3	0	14.55
Combined	9	9	0	14.33
Total	25	27	0	

Note: Largest 23 mm., smallest 11 mm.

of the calculated amount in order to avoid pulmonary congestion and cardiac failure. For those patients having acidosis, the CO_2 combining power of blood was determined on admission, and then alkaline fluid, 1/6 molar sodium lactate solution (or sodium bicarbonate) was given. We usually gave them one-half or two-thirds of the amount calculated according to Hartmann's[5] formula. None of patients developed alkalosis. Besides, the oral administration of potassium alkaline mixture solution was occasionally given to avoid acidosis.

C. Supportive treatment: Blood transfusion was given for severe cases, while vitamins, especially B_1, B_2, and C in daily requirements, dilute saline (0.5 per cent sodium chloride solution), potassium alkaline mixture solution, and orange juice were given generously to supplement the amount of sodium and potassium lost through diarrhea. The amount of food intake depended on the appetite of the individual patient, and was gradually increased up to the normal daily requirements.

Laboratory Studies.—The following routine examinations were made in all cases on admission, and repeated whenever necessary.

1. Stool examination, including macroscopic and microscopic examinations and culture.
2. Streptomycin sensitivity test.
3. Blood examination, including CO_2 combining power.
4. Urine examination, including acetone test.

In fifty-two of the cases streptomycin sensitivity tests were made as soon as the stool cultures revealed the causative organism (in cooperation with Pasteur Institute in Shanghai). The method used consisted of placing on a culture medium, a small round, 5 mm. in diameter, No. 2 filter paper which was previously dipped into a streptomycin solution (500 mg. streptomycin in 1 c.c. buffered phosphate solution at pH 8). When the causative organism was sensitive to streptomycin, there was, after twenty-four hours, a circular zone without growth around the filter paper. By the size of the zone the degree of sensitivity was determined. Sizes larger than 15 mm. are considered as very sensitive, 10 to 15 mm. as moderately sensitive, and those smaller than 10 mm. as not sensitive or resistant. In our fifty-two cases with sensitivity test done, the largest zone without growth was 23 mm., the smallest being 11 mm. Twenty-five of the fifty-two cases were extremely sensitive (48.4 per cent), and twenty-seven cases were moderately sensitive (51.6 per cent). None of the cases showed resistance (Table IV).

Duration of Treatment.—The duration of treatment depended on the response of the causative organism to drugs. Among our cases, except a small number of patients who were discharged after having some improvement, the average duration of treatment was five days in Groups 1 and 2, six days in Group 3, and more than seven days in Group 4 (excluding most of the patients who were discharged with or without improvement).

RESULTS OF TREATMENT

Fever.—The temperature in more than half of the cases in Groups 1 and 2 became normal within two to

three days after treatment; in Group 3, it took three to four days. In Group 4, most of the patients were discharged on request after five days of treatment with or without improvement, except for six patients who recovered whose temperature returned to normal in two to three days (Table V).

Group 4, fifteen patients were discharged after five days of treatment with little or no improvement, and in only six cases was the diarrhea controlled in two to three days (Table VI).

Stools.—Excluding patients who were discharged on request, macroscopic and microscopic characters of

TABLE V. NUMBER OF DAYS FOR CONTROL OF TEMPERATURE TO NORMAL IN TREATED AND CURED PATIENTS

GROUPS	DAYS					
	1	2	3	4	5	OVER 5
Streptomycin A	4	10	7	4	2	
Streptomycin B (after failure of sulfonamides)	3	8	6	4	1	2 16*
Combined	1	3	4	2	2	1
Control	1	3	2	0	2	2

*Cases including improved or unimproved after more than five days' treatment.

TABLE VI. NUMBER OF DAYS FOR CONTROL OF DIARRHEA—TWO OR LESS THAN TWO TIMES DAILY IN TREATED AND CURED PATIENTS

GROUPS	DAYS					
	1	2	3	4	5	OVER 5
Streptomycin A	3	6	8	7	3	1
Streptomycin B (after failure of sulfonamides)	0	7	2	6	3	4
Combined	1	3	3	4	3	2
Control	1	2	3	1	2	15*

*Cases including improved or unimproved after more than five days' treatment.

TABLE VII. NUMBER OF DAYS FOR CONTROL OF NORMAL STOOL IN TREATED AND CURED PATIENTS

GROUPS	DAYS					
	1	2	3	4	5	OVER 5
Streptomycin A	0	8	6	7	5	2
Streptomycin B (after failure of sulfonamides)	2	8	4	7	2	1
Combined	0	2	2	4	4	4
Control	1	2	1	2	1	17*

*Cases including improved or unimproved after more than five days' treatment.

Diarrhea.—When not more than two stools a day were passed the diarrhea was considered as controlled. Excluding a small number of patients in Groups 1, 2, and 3, who were discharged on request or died early, close observation revealed that in most of the cases diarrhea was controlled within two to four days. In the stool became normal after two to four days of streptomycin therapy in Groups 1 and 2; in Group 3, it took four to five days. Stool cultures mostly became negative after two days of treatment. In six cases of Group 4, stool became normal in five days of treatment and seventeen patients were discharged after five or

more days of hospitalization with little or no improvement (Table VII).

Toxic Reaction of Drugs.—In our series, there was not a single case of toxic reaction seen, except for four patients in Group 4 who had nausea, vomiting, and restlessness after administration of sulfonamides.

Condition on Discharge.—In patients receiving streptomycin therapy complete recovery occurred in sixty-seven cases, improvement in sixteen, and death in 12. Nine of the deaths occurred a few hours after admission. The corrected mortality rate for Groups 1, 2, and 3 were 3.3, 3.2, and 4.0 per cent, respectively. In Group 4, nine patients recovered, thirteen showed improvement, two no improvement, and ten died. So the corrected mortality rate was 14.2 per cent (Table VIII).

TABLE VIII. CONDITION ON DISCHARGE

GROUPS	CURED	IMPROVED	DEATH	DEATH WITHIN 24 HOURS	CORRECTED MORTALITY RATE (%)
Streptomycin A	27	2	1	5	3.3
Streptomycin B (after failure of sulfonamides)	24	6	1	0	3.2
Combined	16	8	1	4	4.0
Control	9	15*	4	6	14.2
Total	76	31	7	15	

*Two out of fifteen patients discharged without improvement.

DISCUSSION

Since 1941, the sulfonamide group of drugs has been used for the treatment of bacillary dysentery in children with favorable results.[2, 3, 4] Not only does it shorten the course of illness and reduce the mortality rate, but it also reduces the development of complications. Since 1948, these drugs have been found to be gradually less effective, especially for dysenteric organisms. In recent years because of the progress made in fluid therapy[5, 6, 7, 8, 9, 10] and the introduction of streptomycin, big strides have been made in the treatment of bacillary dysentery in children. Fluid therapy gives favorable influence in severe and moderate cases. In our series, the general condition of the patients improved dramatically within a few hours after treatment. Dehydration and acidosis usually disappeared within one to two days. Pulaski and Amspacher[11] reported ten cases, Levinson and Rayeraft[12] reported sixteen cases of Shigella dysentery treated with streptomycin given either orally or intramuscularly or both with favorable results. Goodfriend and Thurston[13] also obtained excellent results in eighty-eight cases of diarrhea in children. Kane and Foley[14] pointed out that oral administration of streptomycin can suppress the growth of *Bacterium coli* and is more effective than the sulfonamide group of drugs. In our series, it is also evident that streptomycin gives the most favorable effect. In most of the cases, body temperature returned to normal within two to three days; diarrhea was controlled and character of stool became normal in two to four days. The outstanding effect of streptomycin in bacillary dysentery is further evidenced by the fact that in none of our

fifty-two cases did the organisms show resistance in the sensitivity test. Two of the three patients with *S. shigae* infection which has long been known as the most difficult to treat, causing more toxic manifestations, requiring longer duration of treatment, and giving the highest mortality rate as compared with the other organisms, recovered promptly in three to four days. In the third patient who required a longer duration of treatment and who probably already had ulcerative colitis, the body temperature came down to normal after ten days of treatment, and the stools became normal and the diarrhea was controlled in about two weeks. The improvement made by Group 3 was about one day later than the other two groups receiving streptomycin. According to Levinson and Raycraft,[12] combined treatment gave 100 per cent cure in nine cases, oral streptomycin 86 per cent cure in seven cases, and sulfadiazine alone 87 per cent cure in forty-six cases. In our series, streptomycin therapy usually gave a smoother and shortened clinical course. In the group treated entirely with sulfonamides, the results were not so good. We are unable to explain the reason, but if there were more cases in the Levinson and Raycraft series, the result of comparison would be more accurate.

Streptomycin is a quite stable drug, and is not easily absorbed by the intestine after oral administration. This increases the concentration of the drug in the intestine and in turn increases the local sensitivity effect. According to Elias and Durso,[15] the amount of streptomycin excreted from the bowel in those receiving oral streptomycin reaches a high level, at least over 64 per cent, but the concentration of streptomycin in blood does not increase, and the amount excreted from urine is negligible. The intramuscular and intravenous administration of streptomycin gives reverse effects. In our series, streptomycin was given orally as well as intramuscularly.

In our small series of cases employing streptomycin therapy, there was not a single case of relapse or the development of a chronic type, nor were there any instances of drug reaction. Of the three fatal cases, one patient died of chronic malnutrition, and another of complicating pulmonary tuberculosis (based on post-mortem reports). Therefore, although the mortality rate of Groups 1, 2, and 3 appeared to be 3.3, 3.2, and 4.0 per cent, respectively, in reality it may be lower than these figures. The mortality rate of Group 4 was 14.2 per cent, which is several times that of Su and Hsu's report (3.11 per cent) 9 years ago. Furthermore, more than half of the patients in Group 4 were discharged on request with little improvement and two without any improvement. (The long duration of treatment and the low therapeutic effect made the child's parents impatient of remaining in the hospital.) It is possible that the dysenteric organisms are becoming sulfonamide-fast. In the present study, nearly all of the patients were treated successfully with streptomycin. There is reason to believe that the limitation of therapeutic efficacy of streptomycin in severe infections caused by gram-negative organisms arises as the result of bacterial mutation.[16, 17, 18]

The recent report of Chloromycetin in the treatment of three cases of *Shigella sonnei*[19] with dramatic improvement gives us hope that there is yet a better drug to deal with dysentery.

SUMMARY AND CONCLUSIONS

One hundred thirty cases of Shigella dysentery in infants and children with positive stool cultures were studied. Most of the cases (84.6 per cent) occurred in children from 1 to 5 years of age. Males were predominant. Causative organisms were differentiated in 122 cases of Shigella Flexner, among which were 120 cases of Flexner type II (Boyd's type II), three cases of *S. shigae*, four cases of *S. ambigua*, and one case of *S. sonnei*. All the patients were divided into four groups, Group 1 being treated with streptomycin alone, Group 2 with streptomycin after failure of sulfonamides, Group 3 with combined treatment, and Group 4 serving as control (sulfonamides alone). The dosage of streptomycin was 60 to 80 mg. per kilogram per day divided into six doses orally, plus 40 mg. per kilogram per day divided into two, four, or six doses intramuscularly. Fluid therapy and general supportive measures were given as indicated. None of the fifty-two cases showed resistance in the sensitivity test. In most of the cases, including *S. shigae*, body temperature came down to normal within two to three days; diarrhea was controlled and character of stool became normal in two to four days; stool culture usually became negative within two days after streptomycin treatment. The mortality rate was 3.3, 3.2, and 4.0 per cent in Groups 1, 2, and 3, respectively, and 14.2 per cent in Group 4. There was not a single case of relapse or chronicity.

The authors wish to express their sincere gratitude to Dr. Fournier, director of The Pasteur Institute in Shanghai, and his colleagues for so kindly performing the stool cultures of our patients and the sensitivity test of streptomycin to Shigella organisms, and to Dr. H. C. Hou for his kind criticism in the preparation of the manuscript.

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CONGENITAL TRACHEO-ESOPHAGEAL FISTULA WITHOUT ESOPHAGEAL ATRESIA

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INTRODUCTION

THE authoritative publications by Haight,[1, 2] Ladd and Swenson,[3] and others[4, 5] have called attention to congenital anomalies of the esophagus with tracheo-esophageal fistula. The classifications of Vogt[6] and Ladd and Swenson[3] (Fig. 1) have become familiar to most physicians. As experience has accumulated, a preponderance of cases with the type of anomaly comprising a closed proximal esophageal pouch and fistulous communication between the distal esophageal segment and the tracheobronchial tree has been reported. Little if any reference to tracheo-esophageal fistula without esophageal atresia has been made in discussions of congenital esophageal anomaly (Fig. 1*B*). It is believed that this condition, heretofore described so rarely, has certain clinical characteristics which merit emphasis, and we are therefore reporting an illustrative case in detail.

HISTORICAL REVIEW

Cautley[7] in 1917 stated that tracheo-esophageal fistula without esophageal atresia had been recorded only six times. Possibly the earliest report of this anomaly is that by C. F. Richter[8] in 1792, but we have not been able to verify this reference. Lamb[9] in 1873 published the first American article describing the clinical course and post-mortem findings in an infant who lived seven weeks. In the same year Pinard and Tarnier[10] recorded an instance of this condition in a newborn infant who exhibited several other congenital anomalies. Imperatori[11] in 1939 was the first to make an exact preoperative diagnosis and to cure the patient by operation. In 1941 Gengenbach and Dobos[12] reported the post-mortem findings in a 3-month-old infant who, in addition to the tracheo-esophageal fistula, was found to have fusion of the two kidneys on the left side and a patent ductus arteriosus. Two other cases are reported by the same authors but these were not confirmed by operation or post-mortem examination. Haight[13] in 1948 detailed the clinical picture and findings at operation in a 4-year-old child and also reported the post-mortem examination of a patient who succumbed without corrective surgery. Morton, Osborne, and Klassen[14] reported the unusual case of a 26-year-old male whose fistula was apparently congenital. Cardullo and Berens[15] gave the clinical picture, difficulties in diagnosis, and post-mortem findings in an infant who died on the fifth day of life.

Several clinical features of the following case were so outstanding that a diagnosis was made in the first few months of life. A corrective operation which effected an earlier cure than has been previously described was therefore possible.

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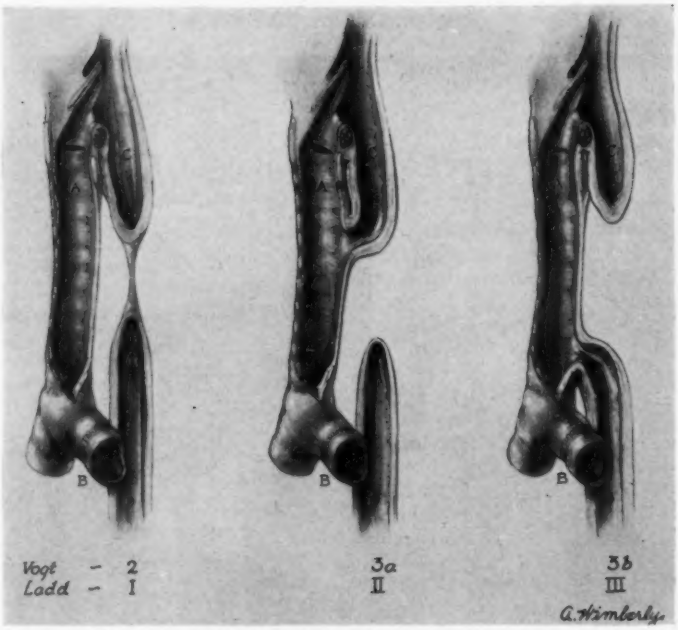


Fig. 1*A*.—Types of tracheo-esophageal fistula as classified by Vogt and Ladd. *A* and *B* indicate the upper trachea and carina, respectively. *C* and *D* are the upper and lower esophageal segments.

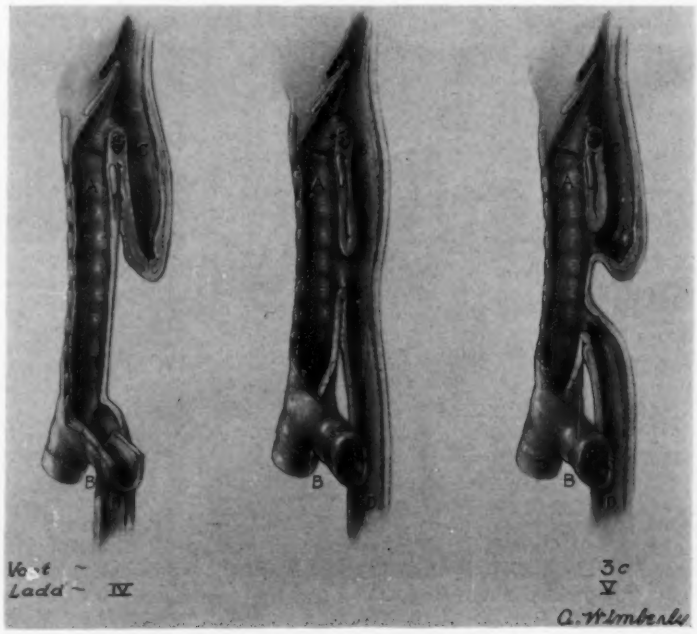


Fig. 1*B*.—Types of tracheo-esophageal fistula as classified by Vogt and Ladd. The center figure is the unclassified and uncommon type exemplified by patient R.M.

CASE REPORT

R. M., a white male, was delivered without complication on Nov. 18, 1949. The birth weight was 7 pounds, 13 ounces, and the prenatal history was negative. On the first day of life there was excessive mucus in the throat resulting in frequent coughing and gagging. After discharge from the hospital on the fourth day of life the infant continued to cough during feeding and often became cyanotic. He did not vomit but there was some spitting up. It was noted that the spitting up was prevented by holding the infant upright for thirty minutes after feeding, and less coughing seemed to result if he was fed with his neck held in a dorsiflexed position.

He was admitted to another hospital within a few weeks, where he was given intravenous fluids and fed by gavage for forty-nine days. Despite this therapy occasional episodes of cyanosis necessitated administration of oxygen.

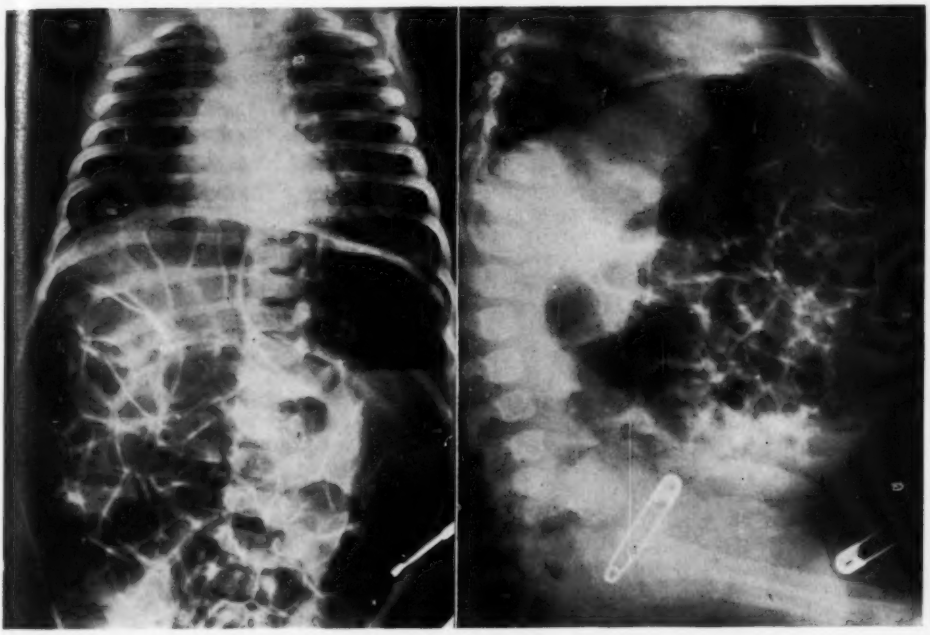
On Feb. 12, 1950, he was admitted to the Children's Hospital. He was poorly nourished, had severe abdominal distention, and was in respiratory distress. A barking type of nonproductive cough often exhausted him. In addition to widespread rhonchi throughout the chest, there were moist râles in the right upper lobe. The blood count and urinalyses gave normal values. Roentgenologic studies showed emphysema and disseminated chronic inflammatory changes in the lungs. There was extreme gaseous distention throughout the gastrointestinal tract (Fig. 2*A*). A barium swallow made with the patient in the supine and the lateral decubitus positions showed no abnormality of the esophagus. Endoscopic examinations disclosed an apparently normal esophagus and only a moderate amount of mucopurulent material in the bronchial tree. Later, on the third bronchoscopic examination, the orifice to the right upper lobe showed inflammatory changes. Gelatin film tests for tryptic activity in the duodenal fluid and the stool revealed active digestion.

As the child was unable to eat well because of shortness of breath and cough, all feedings were given through a polyethylene nasogastric catheter. Penicillin and streptomycin were given parenterally and later aerosol penicillin was added to the therapy. In the first fifteen days of hospitalization the cough abated and the abdominal distention diminished. However, when feeding by catheter was discontinued and food was given by mouth the cough increased and the abdominal distention returned. The infant was discharged on the forty-seventh hospital day having gained only two ounces during his hospital stay.

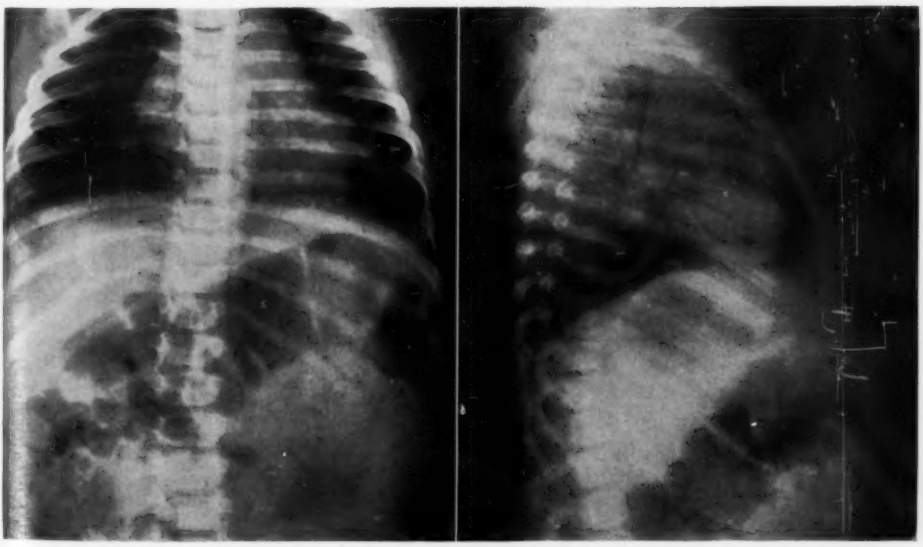
An acute respiratory tract infection occasioned the second admission on April 6, 1950. There was moderate respiratory distress, a persistent cough, and coarse râles were present throughout both lungs. Again, the abdomen was markedly distended. There was a slight leucocytosis; urinalyses gave normal findings. Roentgenologic examination showed disseminated inflammatory changes in both lungs, especially severe in the right upper lobe. Malrotation of the cecum was found on barium contrast study of the gastrointestinal tract.

Aureomycin was given by mouth and penicillin administered intramuscularly and by aerosol. Vomiting did not occur except after strenuous effort in coughing. The infant was discharged on the twentieth hospital day, having gained twelve ounces.

The third admission on May 18, 1950, was for treatment of an acute respiratory tract infection accompanied by choking and cyanosis. Respirations were shallow and rapid, and a harsh croupy cough produced much mucus. Examination of the lungs revealed prolonged expiration with wheezes and showers of râles bilaterally. The abdomen was prominently distended and tympanitic throughout. Laboratory studies were normal except for a slight leucocytosis.



A.



B.

Fig. 2.—*A*, Preoperative roentgenograms which show the extreme gaseous distention of the gastrointestinal tract. *B*, The postoperative roentgenograms show only a normal amount of gas in the small intestine and transverse colon.

Roentgenograms of the chest showed little change from the findings at the previous admission. The films of the abdomen revealed marked gaseous distention of all the intestinal tract except the terminal colon.

Penicillin and aureomycin were administered. Coughing accompanied each feeding of milk and the abdomen remained distended. The infant was observed during a tussive paroxysm to have acute progressive distention of the epigastrium. The coughing produced the effect of a balloon being inflated at this level. On reviewing the history of previous admissions it became apparent that coughing and abdominal distention were severe only when the infant was being fed by mouth rather than by gastric tubes and that the feeding of liquids caused more coughing than when solids alone were given.

A tracheo-esophageal fistula without esophageal atresia seemed the only possible diagnosis in spite of the fact that no fistula had been demonstrated roentgenographically and none had been seen on bronchoscopy. An exploratory thoracotomy was decided upon without further diagnostic procedures and the baby was again fed by a polyethylene catheter inserted into the stomach. Penicillin was given intramuscularly and by aerosol to reduce the infection of the lungs as much as possible.

OPERATIVE NOTE

The patient was anesthetized with cyclopropane administered through an endotracheal system. The right pleural space was entered between the fifth and sixth ribs. There was localized induration at the base of the upper lobe and the apex of the lower lobe. The azygos vein was ligated and divided and the mediastinal pleura opened through a longitudinal incision. At the level midway between the carina and the thoracic inlet a fistulous union between trachea and esophagus was exposed. This short tract with an inner diameter of 8 mm. joined the membranous side of the trachea to the ventral surface of the esophagus. As it was severed, the tracheal opening was closed with interrupted sutures of 5-0 silk. The opening in the esophagus was closed in the same way. The esophageal closure was reinforced with a second row of sutures which passed to the depth of the submucosa only and inverted the first line. The polyethylene catheter remained in the same position after closure. The mediastinal pleura was not sutured. The pleural space was irrigated with saline solution and 200,000 units of penicillin were instilled. Closed drainage of the pleural space was accomplished through two mushroom tip catheters. After the thoracic wall had been closed, a roentgenogram taken immediately confirmed the complete re-expansion of the lung. The blood loss estimated by weighing the soiled sponges was 56 c.c.

The postoperative course was uncomplicated. For six days the infant was fed through the indwelling polyethylene catheter. There was no noteworthy coughing. An esophagram revealed no irregularities and the Lipiodol passed readily into the stomach. The distention of the gastrointestinal tract was greatly reduced (Fig. 2*B*). Seven days after operation the catheter was removed and liquids were given by mouth. Solid food was added on the ninth day and by the eleventh day the infant was taking a complete diet. The wound had healed per primam and the patient was discharged on the twelfth postoperative day. The child has continued to eat well since operation and now at the age of 13 months is a healthy-appearing infant of 26 pounds.

DISCUSSION

Associated symptoms and signs may clearly indicate a tracheo-esophageal fistula without esophageal atresia. Indeed the clinical findings are sometimes so conclusive that surgical treatment may be undertaken without

roentgenologic corroboration of the presence of the anomaly. The physician's lack of familiarity with this condition and his persistent demand for corroborative laboratory evidence often cause delay in establishing the diagnosis; consequently, the patient is exposed to the hazards of additional bouts of aspiration pneumonia.

Paroxysms of coughing precipitated by feeding are the first diagnostic feature. The cough begins shortly after the patient swallows and he may expel a mixture in which the ingested food can be identified. Even in patients as young as the one reported, it is usually possible to ascertain that the less viscid the food, the more severe the bout of coughing. Some solids may be swallowed with negligible difficulty. If oral feedings are discontinued and nutrition is maintained by liquids through a gastric catheter, the cough may almost disappear.

The second diagnostic characteristic is the remarkable gaseous distention of the gastrointestinal tract. The accumulations are much greater than those seen in a normal infant and simple therapeutic measures have no effect upon them. It is believed that in coughing or other forced expiration, part of the air in the trachea is shunted into the esophagus. More or less of the air, depending upon the degree of closure of the cricopharyngeus, is forced into the stomach. Rapid, direct inflation of stomach during coughing is pathognomonic of fistula between the tracheobronchial tree and the upper alimentary tract.

The third clinical characteristic of diagnostic value is the pneumonitis. The aspiration of esophageal contents results in persistent or recurrent pneumonia which is the presenting disease when the patient returns again and again to the physician. A helpful point and one of interest is that the pneumonia most frequently involves the right upper lobe.[16]

It has been stated that if the patient is in the prone position, iodized oil in the esophagus may pass through a tracheo-esophageal fistula more readily than if the patient is upright or supine. However, the failure to visualize a fistula by this method does not exclude the possibility of its existence. Moreover, as infants often aspirate ingested material, a false positive diagnosis may be made when iodized oil is regurgitated from the esophagus and aspirated into the trachea and its branches. The rapid reflux and inhalation may be missed on roentgenograms and intermittent roentgenoscopy. Recently, a 35 per cent solution of Diodrast has been advocated as the ideal agent for tracing tracheo-esophageal communications.[15] The interdiction of barium as a contrast agent is well established.

Endoscopic examination of the esophagus and trachea should be done in every case. Irregularities and natural folds in the mucosa of the esophagus and membranous portion of the trachea may obscure the ostia of the fistula. During bronchoscopy it may be possible to see liquids bubble through the ostium from the esophagus or, if methylene blue has been given by mouth, the colored mucus may more clearly mark the tracheal opening of the fistula. Since endoscopic examination may be the most exact method of determining the level of the fistula, it is essential to the planning of surgical treatment. Imperatori[11] identi-

fied the fistula by this means; in his case a cervical approach was required for definitive surgery. It was clear after endoscopic identification that Haight's case[13] required surgical exposure at the mid-dorsal level. In the case reported, repeated endoscopic examinations showed that the fistula did not involve the trachea or esophagus along the upper third. An approach near the mid-dorsal level was therefore necessary.

Although we have had no experience with the passage of a string in a case of tracheo-esophageal fistula, the nearly disastrous results of others deserve attention. In Imperatori's case the string passed through the fistula only to become coiled as an occlusive mass in the right bronchus. After a somewhat similar complication, D. B. Judd and associates[17] stated that no patient with an esophagobronchial fistula should be given a thread to swallow.

The patients are prepared preoperatively according to the established principles governing the administration of fluid, electrolytes, whole blood and its derivatives. Unstinting effort must be given to the maintenance of a clear oropharynx and to keeping the trachea free of oral and esophageal secretion. The presence of aspiration pneumonia indicates the use of antibiotics with the broadest possible antibacterial effect. If feeding by mouth is discontinued and all food is given in liquid form through an indwelling gastric catheter, nutrition can be maintained and aspiration into the bronchial tree practically eliminated. Interruption of the fistula is the most direct treatment of the pneumonia, hence it must not be delayed.

Reliable closure of the fistula can be made only after adequate exposure of the involved segments of the esophagus and tracheobronchial tree. Experience with the method of endoscopic cauterization of acquired tracheo-esophageal fistulas[18] does not seem to justify its trial in the treatment of the congenital form of fistula. A right extrapleural approach to the mediastinum or a transpleural incision on the right side is made. After division of the fistula, the trachea is closed with closely spaced interrupted sutures of 5-0 silk on an atraumatic needle. The suture line is planned so that the resultant closure is without tension or constriction of the tracheal lumen. The esophagus is then closed in two layers with the same type of suture and material. The first line of sutures is placed through the full thickness of the edges of the esophagus. The second line, placed through the muscularis only, results in inversion of the first row.

Careful attention is given to the reexpansion of collapsed portions of the right lung. The anesthetist slowly and gently increases the pressure in the tracheobronchial tree until all atelectasis has been eliminated. The extrapleural or the pleural space is drained through a system kept closed by a water-seal trap. The patient's nutition may be maintained, as before operation, by liquid diet through a small polyethylene catheter in the stomach. Contrast visualization of the esophagus with iodized oil should be done after the sixth postoperative day. If no abnormality is found, liquids may be given by mouth, and within four days the diet may include all the foods of the child's age group.

SUMMARY

A case of congenital tracheo-esophageal fistula without atresia in a 6-month-old boy is described. This diagnosis should be considered in all infants and children who have recurrent pneumonitis, whose coughing is related to the taking of food, and in whom meteorism is a prominent feature. Observation of the rapid increase of abdominal distention after feeding and coughing is a most helpful corroborative sign.

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THE FUNCTION OF A RECOVERY NURSERY IN A LARGE MATERNITY HOSPITAL

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NEWBORN infants during the first 24 to 48 hours of life frequently require special nursing services due to conditions associated with difficult deliveries, anesthetics, analgesics, and certain operative types of delivery as cesarean sections.

A number of physicians practicing in a large maternity hospital in Houston recognized that the best nursing care for these infants was found in the premature nursery. Infants who were not premature infants in an increasing number were being processed for a few hours in the premature nursery. It seemed logical, therefore, when the new Premature Nursery of the St. Joseph's Maternity Hospital was being constructed, to include a Recovery Nursery to handle full-term infants requiring special nursing attention the first 24 to 48 hours of life. This report is in the nature of a preliminary note on the value of the Recovery Nursery in a large maternity hospital, in which over 6,000 infants are delivered annually.

During the first seven and one-half months the Recovery Nursery of the St. Joseph's Maternity Hospital was in operation, 462 infants weighing 2,500 grams or more were processed. In this period there were 3,351 deliveries of term infants. This percentage of processed infants (13.8 per cent) indicates the importance of the Recovery Nursery to the maternity hospital.

The advantages of such a nursery may be listed under two heads, those accruing to the infant and those to the nursing and medical staffs.

The infant is assured of uniform and specialized care resulting from the individual attention of nurses specially trained for the period of recovery, and the use of special equipment in the nursery.

The new Premature and Recovery Nurseries of the St. Joseph's Maternity Hospital were built in the wing of the maternity hospital which formerly housed the operating rooms used for pediatric surgery. This wing consisted of a rotunda around which were three large operating rooms, a sterilizing room, two large closets containing equipment for the operating rooms, and an instrument room. These rooms were redesigned to function as a Recovery Room, with six incubators, an Air-Lock, and two bassinettes. Two premature nursery rooms were furnished with twenty incubators, an Air-Lock, and seven bassinettes. Electrical outlets were provided for each incubator. Oxygen is piped into the rooms from a central source in the basement of the hospital. Compressed air is piped in for the Air-Locks. The former sterilizing room was converted into a small room for clyses, surgery, and transfusions. The former instrument room was made into a room for supplies and an electric refrigerator installed for formulas. The entire plant was air-conditioned with air being forced into the nurseries and then exhausted by a large fan from the rotunda around which the nurseries were located.

From the Departments of Pediatrics of the St. Joseph's Maternity Hospital and Baylor College of Medicine.

The Recovery Nursery has a telephone and a small bathroom making is unnecessary for the nurse on duty to ever leave her station. Examining flood light and sterilamp are placed over the doorway. The examining physician examines the infant on a table which is swung into the doorway under the flood light. Two scrub basins are located in the rotunda immediately off the nurseries in which the physician scrubs his hands and enters a gown before examining the infant.

The nursing care given to the infant in the Recovery Nursery is furnished by nurses particularly trained in the problems of the term infant occurring during the first 24 to 48 hours of life. It is a standing order that all infants in difficulty coming from the delivery room or going "bad" on the regular nursing floors are to be taken immediately to the Recovery Nursery. All necessary emergency steps are taken by the nurse on duty while the physician or pediatrician in charge is being contacted.

The physician benefits from the Recovery Nursery in that he has the assurance that his patient will receive proper and special nursing care until he is contacted. His patient is always in the same locality in the hospital.

The nurses benefit from the Recovery Nursery in that they have at their disposal everything that is necessary to give adequate and intelligent handling of the infant. As the oxygen is piped from a central source, there is no searching and moving of oxygen tanks. An Air-Lock is available for specialized problems. The physical plant is adjusted to provide adequate isolation technique.

The hospital benefits from the Recovery Nursery in that its patients are assured the maximum opportunity of survival which, of course, lowers the neonatal death rate. In addition, a means is furnished for training students so that they will have adequate knowledge of the management of the term newborn infant in distress in the immediate newborn period.

The mortality rate of the term infant has dropped from 6.2 to 5.3 per thousand live births since the use of the Air-Lock in resuscitation and the management of the handicapped newborn term infant localized in a special Recovery Nursery. This is in line with the observed decrease in the premature mortality rate[1] when a premature nursery with trained personnel is installed in a hospital.

SUMMARY

1. A Recovery Nursery to handle problems of the term infant in distress immediately after delivery has proved its value to a large maternity hospital. This nursery has been used in 13.8 per cent of term infants delivered over a period of seven and one-half months.

2. It has been found that the Recovery Nursery can function together with a Premature Nursery and the same plant can contain both.

3. The combination of the physical plant of the Premature Nursery and a Recovery Nursery will provide enough population to stabilize the nursing personnel and fill the hospital space that may be available in the small or large hospital that could not be filled adequately by either a Premature Nursery or a Recovery Nursery alone.

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Case Reports

TYPE F HEMOPHILUS INFLUENZAE MENINGITIS

Case Report With a Review of the Literature

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THE identification of six specific types of *Hemophilus influenzae*, a, b, c, d, e, and f, was reported by Pittman[1] in 1931. Almost all cases of *H. influenzae* meningitis are caused by the specific type b organism, according to Neter.[2] Alexander and associates[3, 4] point out that an occasional case is caused by a type a or f organism. Martinez and Juan,[5] in reviewing a bacteriologic study of purulent meningitis in children, found that in thirty-one typed cases of *H. influenzae* meningitis, one was caused by a type f organism and the remainder were due to type b. At the Kingston Avenue Hospital, during the period from January, 1939, to June, 1949, all twenty-seven cases of *H. influenzae* meningitis were typed. Of these, all except the case reported in this paper were caused by the type b organism.

The following case report of a type f *H. influenzae* meningitis emphasizes the need for re-evaluating the role of penicillin in treating type f *H. influenzae* infections.

CASE REPORT*

J. D., a semicomatose 10-month-old white female weighing 23 pounds, was admitted to the Kingston Avenue Hospital on Feb. 16, 1949. One week prior to admission the infant "developed a cold." During the three days before hospitalization the parents noted an increasing somnolence and stiff neck. The temperature ranged between 100° and 103° F. The past history and family history were noncontributory. On admission the temperature was 102° F. Physical examination disclosed an acutely ill infant, aroused only by painful stimuli, and maintaining an opisthotonic position. A bulging, tense anterior fontanel and marked nuchal rigidity were present. The pupils were constricted and reacted poorly to light. The pharynx was moderately injected. Examination of the heart and lungs was essentially negative. Positive Brudzinski and Kernig signs were elicited. A questionable bilateral Babinski sign was present. The patellar reflexes were hyperactive. A spinal tap performed immediately on admission disclosed cloudy fluid under greatly increased pressure. The cell count revealed 12,800 cells per cubic millimeter mostly polymorphonuclear leucocytes. The total protein was 76 mg. per cent; the sugar was 22 mg. per cent. A direct smear revealed many pleomorphic gram-negative bacilli. The initial blood count showed 8.5 Gm. hemoglobin, red blood cell count 2,450,000, white blood cell count 7,300, with a differential of 28 per cent polymorphonuclear leucocytes, 66 per cent lymphocytes, and 6 per cent monocytes. A faint trace of albumin was found on urine analysis.

Therapy on admission consisted of penicillin, 100,000 units intramuscularly every three hours, and sulfadiazine, 1 Gm. immediately and 0.5 Gm. orally every four hours. Frequent clyses of 5 per cent glucose in normal saline were administered. On February 17, the second hospital day, the temperature was normal but the infant was still irritable. A positive spinal fluid culture for *H. influenzae*

*From the Service of Dr. Kenneth Jennings, Communicable Disease Division, Kingston Avenue Hospital.

was reported on the third hospital day. However, a negative Quellung reaction resulted with type b *H. influenzae* typing antiserum. Subsequently, positive agglutination with type f specific antiserum was reported by the Research Laboratory of the New York City Board of Health.

With the positive laboratory report of *H. influenzae* meningitis, penicillin was discontinued on February 18, and streptomycin, 0.5 Gm. intramuscularly twice daily, was promptly instituted. Fluids were still being taken poorly by mouth, and frequent supplemental clyses were administered. During the following four days the temperature curve was spiking in nature and ranged from 100° to 103.6° F. On February 21 penicillin therapy, 100,000 units initially and 50,000 units intramuscularly every three hours, was reinstituted. The temperature promptly dropped and in two days the infant was afebrile. Supplemental parenteral fluid administration was discontinued in view of an adequate oral intake. Nuchal rigidity had regressed almost completely, and the anterior fontanel was neither tense nor bulging. On February 24 streptomycin and sulfadiazine therapy were discontinued. Aqueous penicillin was supplanted by procaine penicillin G in sesame oil suspended with 2 per cent w/v aluminum monostearate, 300,000 units intramuscularly once daily for four days, and then every second day for a week.

From February 24 until discharge from the hospital on March 24, the patient remained afebrile. A lumbar puncture on March 1 revealed clear fluid under normal pressure. The cell count was 184 lymphocytes per cubic millimeter, total protein 51 mg. per cent, and sugar 52 mg. per cent. Direct smears and spinal fluid cultures were negative for organisms. On March 22 lumbar puncture revealed 134 lymphocytes per cubic millimeter, total protein 58 mg. per cent, and sugar 50 mg. per cent. Cultures remained sterile. On March 24, 1949, the patient was discharged after a hospital stay of thirty-seven days.

One month after discharge a follow-up physical examination was completely negative. At this time lumbar puncture revealed clear fluid under normal pressure. A cell count disclosed 47 lymphocytes per cubic millimeter. The spinal fluid chemistries were as follows: total protein 29 mg. per cent; sugar 62 mg. per cent; chlorides 665 mg. per cent. A direct smear and culture of the spinal fluid were negative for organisms.

Through the cooperation of Dr. H. E. Alexander and Miss Grace Leidy, sensitivity studies of our patient's strain of type f *H. influenzae* were conducted at the Babies Hospital of the Columbia-Presbyterian Medical Center in New York City. The antibiotics were incorporated in Levinthal agar to yield final concentrations of 0.5, 1.0, 3.0, 5.0, and 10.0 μg (streptomycin) or units (penicillin) per milliliter. The inoculum was a 2 mm. loopful (approximately one million organisms) of a six-hour Levinthal broth culture. The minimal effective concentration of streptomycin was 3 μg per milliliter, and of penicillin, 3 units per milliliter.

DISCUSSION

Parke[6] reported a case of *H. influenzae* meningitis caused by the type f organism in a 5-year-old child. This patient received a course of sulfadiazine, and when the temperature remained elevated, penicillin and sulfathiazole were given, resulting in a normal temperature and ultimate recovery. The author concluded that the course of penicillin probably did not contribute to the patient's recovery since this antibiotic "does not ordinarily affect *Hemophilus influenzae.*" However, a possible synergistic role with the sulfonamide drugs was mentioned.

On the other hand, Hewitt and Pittman,[7] in testing the in vitro effect of penicillin X and G on *H. influenzae,* felt that this antibiotic prevents or in-

hibits the swelling of the capsule of the bacillus and is injurious to it. This may interfere with the ability to type *H. influenzae* in patients who previously have received penicillin therapy. In vitro streptomycin was found to be the most effective drug, and penicillin X was superior to penicillin G. Type f *H. influenzae* was sensitive to 0.18 to 0.37 unit of penicillin X per milliliter and to 0.18 to 1.5 units of penicillin G per milliliter. Streptomycin inhibited the type f organism in a concentration of 2.5 to 5.0 μg per milliliter. Alexander[8] found that streptomycin completely inhibited type b *H. influenzae* in concentrations between 0.8 and 10.8 units per milliliter and that a few cultures of types a, e, d, e, and f exhibited a comparable degree of sensitivity. Alexander and Leidy[9] point out that streptomycin is effective against all six types of *H. influenzae* as well as the nontypeable variety of this organism, and that the therapy of choice in *H. influenzae* infections is streptomycin and sulfadiazine, with type-specific antiserum added in treating infants under the age of 6 to 7 months.

Nevertheless, the proved susceptibility of *H. influenzae* type f to penicillin would suggest that combined treatment with streptomycin, sulfadadiazine, and penicillin be considered in all cases of type f *H. influenzae* meningitis. The clinical response of our patient was very apparent after the reintroduction of penicillin to the therapeutic regime. Parke's case as well exhibited a similar clinical response with the addition of penicillin to the therapy.

Menngitis due to *H. influenzae* is an uncommon disease. However, it was felt that information concerning its over-all incidence might be of interest. Accordingly, all cases of meningitis during the ten-year period, 1940 through 1949, were tabulated (Table I). It can be seen that, so far as *H. influenzae* meningitis is concerned, the five-year period of 1945 through 1949 has recorded not only a relative, but an absolute, increase in the number of cases.

TABLE I. TYPES OF MENINGITIS AT KINGSTON AVENUE HOSPITAL (1940-1949)

YEAR	TOTAL CASES OF MENINGITIS	H. INFLUENZAE	N. MENINGITIDIS	M. TUBERCULOSIS	D. PNEUMONIAE	LYMPHOCYTIC	STREPTOCOCCUS (ALL TYPES)	SALMONELLA	ETIOLOGY UNKNOWN
1940	5	1	1	0	1	1		0	1
1941	10	0	8	1	0	0	0	0	1
1942	24	1	19	1	0	1	0	0	2
1943	90	0	83	3	2	1	0	0	1
1944	83	2	71	2	3	1	1	0	3
1945	70	6	61	2	1	0	0	0	0
1946	49	4	39	4	1	0	0	0	1
1947	19	3	7	5	0	0	0	0	4
1948	14	3	5	2	0	0	1	1	2
1949	25	10	6	2	1	0	0	0	6

Since total numbers are small, sweeping conclusions are not justified. It may be that the general use of sulfonamide and antibiotic drugs in febrile states has resulted in aborting or preventing meningitis due to organisms such as the meningococcus which are susceptible to these agents. This in turn may be now shifting the balance in the direction of those organisms less readily inhibited by modern therapy. Further experience is necessary, however, before definite conclusions can be drawn.

SUMMARY

1. A case of type f *H. influenzae* meningitis in an infant 10 months of age was presented.

2. Clinical recovery was enhanced after the addition of penicillin to the therapeutic regime of sulfadiazine and streptomycin.

3. A review of the literature was presented with particular reference to the in vitro sensitivity of the type f *H. influenzae* to antibiotics.

4. Within recent years there has been a relative and absolute increase in meningitis due to *H. inflenzae* of all types.

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INTRACRANIAL CALCIFICATION FOLLOWING PNEUMOCOCCIC MENINGITIS

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IT IS the purpose of this paper to report a case of pneumococcic meningitis in an infant, which was followed by intracranial calcification.

Pathologic intracranial calcification may occur as the result of various disease processes. Neoplasms such as meningiomas, ependymomas, craniopharyngiomas, teratomas, dermoids, angiomas, oligodendroglias, astrocytomas, and gliomas sometimes show areas of calcification.[1] Subdural hematomas, intracerebral hemorrhages, old brain abscesses, and cerebral aneurysms sometimes become calcified. In syndromes such as tuberous sclerosis, Sturge-Weber syndrome, progressive facial hemiatrophy, and Krabbe's disease, areas of cerebral calcification are seen often enough to be considered characteristic. Metazoan diseases such as echinococcus cysts, cysticercus cellulosae, and trichinosis may also give rise to cerebral calcification. Intracranial tubercles and syphilomas may calcify. Hyperparathyroidism may be associated with calcification of meningeal and cerebral vessels. More recently, symmetrical cortical calcification has been described with parathyroid insufficiency.[2] Toxoplasmosis, a protozoan infection, is another cause of cerebral calcification which has recently been studied.[3] Among the rare causes of intracranial calcification are carbon monoxide poisoning, encephalitis, and meningo-encephalitis.

CASE REPORT

C. P., a 2-month-old Puerto Rican female, was admitted to the Children's Division of the Cook County Hospital on April 13, 1949, because of hoarseness, cough, sniffling, anorexia, loose stools, occasional emesis, and irritability of several days' duration. The mother was a gravida iii, para iii. The other siblings were living and well. Prenatal, birth, and previous history of the mother and patient were uneventful. Physical examination on admission revealed a somewhat lethargic female infant with a rectal temperature of 101.2° F. and a slightly injected pharynx. A short, generalized convulsion accompanied by nystagmus occurred during the initial examination. Lumbar puncture revealed cloudy fluid, 782 cells, 4 plus Pandy, gram-positive diplococci on smear, later identified as pneumococci on culture; glucose 14 mg. per 100 c.c., protein 304 mg. per 100 c.c., chlorides 100 meq. per liter, negative Kahn. The following day the patient appeared comatose, and the anterior fontanel was bulging. Frequent episodes of twitchings of the extremities occurred. Positive Kernig's and Brudzinski's signs, and pin-point pupils were observed at times. Funduscopic examination was negative. The patient gradually became more alert but developed generalized rigidity which was the outstanding finding when discharged on July 29, 1949, after three and a half months' hospitalization. Treatment consisted of intravenous fluids, blood transfusions, intramuscular streptomycin, oral aureomycin, sulfadiazine (intravenously at first, then subcutaneously, finally orally), and intramuscular aqueous penicillin.

In addition to the initial lumbar puncture, subsequent lumbar punctures were done. The cerebrospinal fluid gradually became normal. Mantoux 1:10,000 was negative. X-ray of

From the Children's Division of the Cook County Hospital.

the skull taken two weeks after admission was negative (Fig. 1).

The patient was readmitted on Nov. 2, 1949, at the age of 9 months because of cough, anorexia, and rolling of the eyes of three days' duration. The mother stated that the patient had not attempted to sit, stand, or crawl, and did not cry. She believed that the patient could neither hear nor see. There had been frequent episodes of generalized convulsions and dyspnea. Physical examination on admission showed a rectal temperature of 105° F., opisthotonos, generalized spasticity and rigidity, intermittent twitchings of the right hand and foot, and nystagmus. Head circumference was 15 inches, chest circumference 17½ inches. There was overriding of the sagittal suture posteriorly. Dullness and râles were noted over the left lower pulmonary field. X-ray films of the chest demonstrated a left lower lobe pneumonia. Lumbar puncture revealed clear fluid, 310 white blood cells, negative Pandy, Kahn, smear, and culture; glucose 80 mg. per 100 c.c., protein 16 mg. per 100 c.c. Eye examination showed fixed pupils of equal size, aimless and at times divergent movements, and pale discs which were suggestive of optic atrophy. The patient remained in the hospital for two and one-half months during which period the pulmonary findings cleared. The neurological findings, however, were the same as on admission. Treatment consisted of oral sulfadiazine, intramuscular streptomycin and procaine penicillin. Pertinent laboratory findings subsequent to the initial lumbar puncture were negative cerebrospinal fluid at the time of discharge, negative Mantoux 1:10,000, negative complement fixation test for toxoplasmosis (performed by the National Institute for Health, Bethesda, Md.). X-ray of the skull on second admission showed several large, irregular, mottled, calcific densities in the right temporoparietal region with very small densities in other parts of the skull. There was overlapping of the bones at the sagittal plane with asymmetry of the skull (Figs. 2 and 3). Pneumoencephalography revealed dilatation of the right lateral ventricle, multiloculated distribution of air in

Fig. 1.—Negative skull x-ray two weeks after first admission.

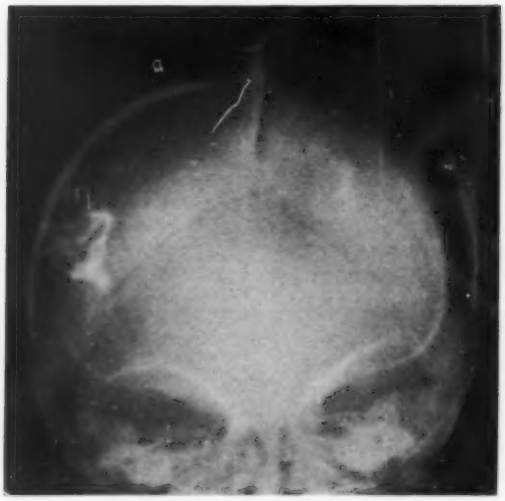

Fig. 2.

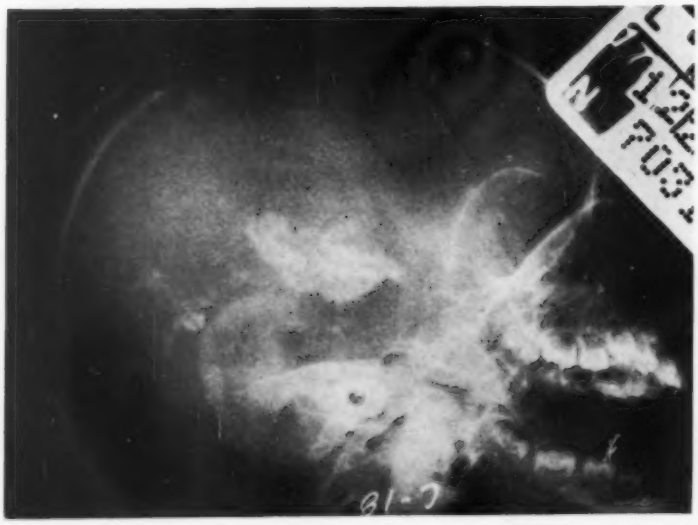

Fig. 3.

Figs. 2 and 3.—Skull x-rays seven months following meningitis, showing calcific densities and overlapping of bones.

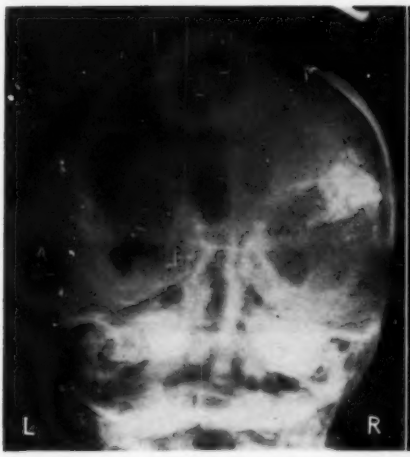

Fig. 4.

Fig. 5.

Fig. 4.—Pneumoencephalogram (anteroposterior view) showing multiloculated distribution of air over left frontoparietal and calcific densities in right temporoparietal regions.

Fig. 5.—Pneumoencephalogram (right lateral view) showing dilatation of right lateral ventricle and calcific densities.

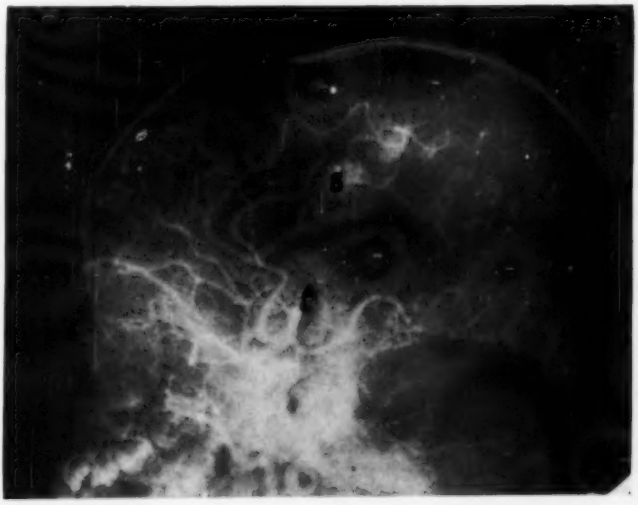

Fig. 6.—Cerebral arteriogram showing (*A*) thrombosis of middle cerebral artery, and (*B*) calcific densities distal to it.

the left frontoparietal region, and calcific densities as previously described (Figs. 4 and 5).

Between April 18, 1950, and May 2, 1950, the patient (14 months of age) was rehospitalized for re-evaluation. She was found to be deaf, blind, did not cry, crawl, sit, or stand. There was generalized rigidity and spasticity. Head circumference was 15 inches, chest circumference 18 inches. There was overlapping of the right frontal bone over the right parietal bone. Frequent generalized convulsions were noted. Blood calcium was 10.7 mg. per 100 c.c., inorganic phosphorus 5.2 mg. per 100 c.c., alkaline phosphatase 4.5 Bodansky units. Cerebral arteriography, performed by Dr. G. W. Smith of the neurosurgical department, showed lack of filling of the middle cerebral artery distal to the bifurcation (Fig. 6). This was interpreted as thrombosis of the middle cerebral artery with areas of encephalomalacia and calcification distal to the thrombosis.

DISCUSSION

Cerebral calcification has been reported as a rare sequel to encephalitis lethargica,[4] also following poliomyelitis[5] and meningo-encephalitis.[6, 7] Camp states that in the absence of associated encephalitis, calcification from meningitis per se is rare.[8] Meningitis is often associated with encephalitis. It has been held by the senior author for many years that many clinical findings in meningitis must be explained on the basis of associated encephalitis.[9] He has also observed encephalomalacia in some cases of purulent meningitis. Wertham, studying autopsy specimens of brains of patients who had died of purulent meningitis, found infiltrations, hemorrhages, small abscesses, and hemorrhagic purulent encephalitic foci away from the meningitic process in the cortex.[10] Eicke found thrombosis of arteries and veins and inflammatory involvement of the brain substance in meningitis.[11]

In reviewing our case, the question arose whether the areas of calcification which were demonstrated roentgenographically following the course of the meningitis were also present before. Their absence, however, is shown by x-rays shortly after the onset of the disease. Toxoplasmosis, cerebral neoplasms, hypo- and hyperparathyroidism, syphilis, tuberculosis, and other causes of intracranial calcification were ruled out by appropriate laboratory procedures and the clinical picture and course. The meningoencephalitic process also is evident by the clinical course of the patient who, after the acute intracranial infection had cleared, was left with microcephalus, generalized spasticity, convulsions, and general retardation. Permanent central nervous system damage following pneumococcic meningitis despite chemotherapy and antibiotics is not unusual.[12, 13]

The pathogenesis and the location of the calcification in our case cannot be definitely established. There are four possibilities: (1) thrombosis of the middle cerebral artery with encephalomalacia and subsequent calcification, (2) intracerebral calcification following meningitis without thrombosis, (3) subdural hematoma with subsequent calcification following meningitis, and (4) calcification of the meninges following meningitis. We are mainly interested in reporting the occurrence of intracranial calcification following meningitis.

SUMMARY

Intracranial calcification following pneumococcic meningitis has been presented. Clinical sequelae were generalized spasticity and rigidity, convulsions, and severe mental retardation. Cerebral arteriography revealed thrombosis of the middle cerebral artery. The pathogenesis of the calcification, difficult to evaluate in this case, has been discussed.

Addendum

The patient was hospitalized from Jan. 9, 1951, to Feb. 27, 1951, at the

age of 23 months. There were no significant clinical changes. Laboratory studies including x-rays and pneumoencephalograms were as previously described.

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LOCAL HEMORRHAGIC-NECROTIC SKIN REACTION FOLLOWING PENICILLIN

Review of Literature and Case Report

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ALTHOUGH there have been numerous reports of reactions to penicillin in the literature, the following case report presents such a drastic local reaction that its publication seems justifiable.

REVIEW OF LITERATURE

Reynolds and Moore[1] in a recent review of the toxic reactions to penicillin following treatment for syphilis indicate that the reactions have been largely restricted to allergic manifestations, and are most often dermal sensitizations. They list the following reactions: allergic dermatosis, serum sicknesslike reactions, anaphylactic shock, febrile reactions, exfoliative dermatitis, agranulocytosis, purpura, jaundice, and Herxheimer reactions.

May[2] reports a case of aseptic necrosis following intramuscular injections of penicillin into the thighs. The symptoms consisted of burning pain, redness of skin and induration at the site of the injections. Ten days after the beginning of the treatment, fluctuant swellings developed in the muscles. The thighs were incised and sterile pus was obtained. A slough occurred in both thighs, and the area slowly epithelized. Procaine and penicillin intradermal sensitivity tests were negative.

Chu and Cutting[3] report the case of a physician, who, after repeated injections of penicillin in oil and beeswax followed by aqueous and oral penicillin, showed urticaria, followed by red, tense swellings, which became orange-blue, painful to touch, and looked as though they would become necrotic. The reaction subsided in two weeks. The local reactions according to the authors appeared to be typical Arthus reactions and were reproduced in rabbits receiving penicillin alone. They note that the most common clinical manifestations have been urticaria, angioneurotic edema, vesicular, bullous, or papular eruptions, contact dermatitis, Arthus type of reaction, and serum sickness.

Hopkins and Lawrence[4] report two patients with gluteal reactions on about the fourteenth day of intramuscular injections of penicillin in beeswax and oil. Huge, indurated, and tender lesions developed in the buttocks. The overlying skin was dusky. The lesions, which resembled Arthus phenomenon, subsided in two or three days with heat. They suspected some fault in melting the penicillin preparation.

Mears and State[5] present a patient, who, following a radical mastectomy, received injections of penicillin in wax and oil. Later the wound was treated with local wet dressings of penicillin. There was a wound reaction in the form of a nonpurulent, necrotizing, intense inflammatory process spreading rapidly. The wound finally healed by granulation. This patient also developed a generalized urticaria. They report this reaction as an Arthus reaction.

Rostenberg and Welch,[6] in a study of the types of hypersensitivity induced by penicillin, report that 5 per cent of 144 individuals tested with crystalline penicillin sodium exhibited positive reactions of the tuberculin type, despite the fact that none had had any prior contact with penicillin. Repeated multiple injections of penicillin sodium caused the development of reactions of the Arthus type in some individuals, while others developed a tuberculin type of hypersensitivity.

Romansky,[7] in a review of 4,000 cases receiving 60,000 injections of calcium penicillin in beeswax and peanut oil, indicates only two instances of sterile foreign body abscess. There was an incidence of 5 per cent allergic reactions varying from slight urticaria to angioneurotic edema. He also states that in infants a nodule may be palpable for some time, since the penicillin may have been given subcutaneously.

ture rose to 101.2° F. On the day following the onset of symptoms, a confluent erythema developed over the entire buttocks and an area of induration could be palpated. Recovery occurred following the withdrawal of penicillin.

CASE REPORT

J. P., a 6-month-old white female infant, was seen on May 17, 1950, with a temperature of 103° F. of one day's

Fig. 1.—Lesion as it appeared on June 8, 1950, about one week after the slough.

Boelter and Hatoff[8] observed a reaction of the Shwartzman type in a 10-year-old girl suffering from an aspiration pneumonia. The patient had received penicillin in oil intramuscularly every twelve hours for nine days. On the tenth day, treatment was changed to aqueous penicillin intramuscularly. After two doses the patient complained of pruritis and developed sixteen to eighteen indurated, nontender, urticarial wheals on the buttocks. Each of the wheals surrounded a puncture site where penicillin in oil had been injected. The child began to complain of severe pain following each injection of penicillin. Slight ptosis of the right eyelid supervened, and her temperature duration. The baby was somewhat fretful, but had no other symptoms. Three hundred thousand units of Lentopen* had been injected into the buttocks about six weeks earlier for an upper respiratory infection, with an uneventful recovery. There have been no other illnesses and no history of allergy.

Examination revealed a rectal temperature of 103° F., and a moderately injected pharynx. The remainder of the examination was essentially negative. The patient was given 300,000 units of Lentopen intramuscularly in the right buttock. Immediately after

*Wyeth's Procaine Penicillin in Peanut Oil and Aluminum Stearate.

the injection there was a blanching of the skin, followed in an hour by a reddish purple discoloration, about the size of a silver dollar, at the site of the injection. The area gradually became more swollen, tender, and purple, and was followed by a hemorrhagic streaking of the skin, branchlike in character, extending upward to the lumbosacral region, and downward on the posterior surface of the thigh to the knee. The streaking resembled a lymphangitis, but was more hemorrhagic. This was extremely painful as evidenced by continuous crying and fretting for three days, in spite of sedation, cold packs, and antihistamine therapy. The streaked areas gradually subsided in a month's time. The central lesion became deeper in color, formed blebs, and after two weeks finally broke down. The area in the buttock completely sloughed out. There was a slight serous discharge, but at no time were there any evidence of pus. The child's temperature became normal within forty-eight hours.

Surgical consultation was obtained with follow-up care consisting of daily sterile petroleum jelly dressings. The wound healed by granulation, and on June 17, 1950, several small pinch grafts were applied. Two weeks later the area was completely healed. The entire course of this reaction lasted about six weeks.

On July 6, 1950, scratch tests were done with aluminum stearate gel, peanut oil, procaine penicillin G, and potassium penicillin G. There was no reaction to aluminum stearate gel or peanut oil. Procaine penicillin G gave an area of erythema about 1 cm. in diameter, while potassium penicillin G produced an area of erythema about 2 cm. in diameter. There were no pseudopods present. Two per cent procaine, used locally during the skin grafting, gave no reaction.

DISCUSSION

In attempting to classify the reaction reported in this case, most of the literature has been reviewed and a considerable difference of opinion has been found as to whether the hemorrhagic-necrotic reactions should be called Arthus phenomenon or Shwartzman phenomenon. In 1903, Arthus reported that, following successive weekly subcutaneous injections of an antigen, such as horse serum, edema gradually developed at the site of the inoculation, followed by induration, which sometimes went on to necrosis and aseptic ulceration. It appeared after the third injection, and the injections were not made at the same site. It has been shown that local anaphylaxis of the Arthus phenomenon may occur in any organ of a sensitized animal following direct contact with the antigen.

In 1928, Shwartzman[10] injected *B. typhosus* toxin intradermally into the skin of a rabbit followed in twenty-four hours by an intravenous injection of the same filtrate. Four hours later there was a severe hemorrhagic-necrotic lesion at the site of the previous intradermal injection. Histologically, there was destruction of all cells in the area, hemorrhage into the surrounding tissues, and platelet thrombosis of the small vessels.

Harkavy and Romanoff[11] in comparing the Shwartzman phenomenon with the Arthus phenomenon show the following differences. Arthus is produced by nonbacterial soluble proteins, such as horse serum, egg albumin, and casein. To produce the Arthus phenomenon it is necessary to give repeated subcutaneous injections at intervals of several days. Sensitization persists for a long time, in contrast to the Shwartzman phenomenon, which cannot be elicited after 120 hours following the preparation of the skin site. The Arthus phenomenon can be induced either intravenously or subcutaneously, whereas in the Shwartzman reaction the second injection must be intravenously. Arthus reaction is absolutely specific, produced only by homologous antigen injected into a normal animal, while no such specificity is needed for the Shwartzman reaction. Their cases represent the occurrences of local hemorrhagic necrosis in skin

sites of known allergic individuals. The authors challenge the cases reported as Arthus phenomenon.[12] They feel that the cases were probably instances of the Shwartzman phenomenon. They conclude that bacterial infections prepare the tissues of the individual for subsequent attack by homologous or heterologous bacteria of unrelated antigen-antibody complexes, bringing about local or general tissue damage.

There are those who have felt that possibly the Arthus phenomenon does not occur in man and that all extensive hemorrhagic reactions at the site of antigen injection should be considered examples of the local Shwartzman reaction.[13]

Black-Schaffer[14] feels that the differentiation of the two phenomena may be difficult. The histologic differentiation is not reliable. The Shwartzman reaction is shown by necrotizing thrombophlebitis and arteritis as well as hemorrhage and eventual necrosis of the dermis and epidermis; the same is true of the Arthus reaction, though to a lesser degree. However, clinically, a hypersensitive individual may show as severe a reaction to an antigen as could occur in a Shwartzman phenomenon. It is apparent that most of the reactions occur during acute infections and not in the course of prophylactic therapy.

Harkavy[15] states that although it is true that the original Shwartzman phenomenon in the experimental animal could not be elicited after 120 hours, later reports have modified this point of view. He quotes Black-Schaffer[14] extensively to substantiate the case for a Shwartzman reaction in this report. He believes that the first injection of Lentopen antigen represented the primary sensitizing dose. The acute pharyngitis acted as the focus of infection from which bacteria were disseminated and became localized at the site into which the second dose of antigen, Lentopen, was injected. At this site a Shwartzman phenomenon ensued, mediated by an anaphylactic reaction due to the reinjected Lentopen, and preformed corresponding antibodies resulting from the previous injection of Lentopen.

This paper would not be complete without mention of embolia cutis medicamentosa as a third and very formidable explanation for the reaction occurring in the case report. The first instances of arterial embolism or embolia cutis medicamentosa were reported in 1923 by Freudenthal[16] from the injection of bismuth preparations. Gammel[17] was the first in this country to report an arterial embolism following the intramuscular injection of bismuth. Later Sulzberger and Baer[18] added more cases following the injections of heavy metals for the treatment of syphilis.

Immediately or shortly after the supposed intramuscular injection of an insoluble mercury or bismuth salt, the patient develops malaise, high fever, and complains of a violent pain radiating into the leg. There is a diffuse swelling of the gluteus muscle, with a bluish red, marmoraceous, netlike discoloration of the skin near or around the injection site. The discolored skin may become necrotic. The clinical picture may be the same after the intra-arterial injection of soluble preparations. In this instance the obstruction of the blood vessels is due to an endarteritic thrombosis.

On histologic examination, in the case of intra-arterial injection with bismuth, the cutaneous arteries are blocked with needle-shaped crystals of bismuth subsalicylate. The streaked violaceous discoloration is presumably due to an escape of hemoglobin into the finer arterioles.

This condition is a rare accident and perhaps in an occasional instance unavoidable. In many of the reported cases aspiration was performed, and even though no blood was seen, this complication followed. According to Gammel,[17] this safeguard is not sufficient when tenacious, creamlike suspensions are injected. It is probable that the viscosity of the drug prevents the backflow. He suggests that the needle be first inserted separately;

after an interval of at least fifteen seconds the syringe should be attached, and after aspiration, the injection is completed. Even with this precaution it is suggested that unintentional intra-arterial injections will occur.

In the present case, even though the usual precautions of withdrawing before injecting were carried out, one cannot be certain that one of the finer vessels was not injected. If this case is to be considered one of embolia cutis medicamentosa, then it is thought to be the first one reported in the literature. If this case is an anaphylactic reaction, then I would interpret it as a Shwartzman phenomenon, since this occurred in an infant, who was acutely ill, who had received a sensitizing dose of penicillin six weeks prior to the present illness, and who had a subsequent injection of penicillin.

SUMMARY

1. Penicillin reactions as reported in the literature are reviewed.

2. A case is reported of a severe hemorrhagic-necrotic lesion occurring following a penicillin injection.

3. Arthus phenomenon, Shwartzman phenomenon, and embolia cutis medicamentosa are discussed as possible diagnoses.

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Clinical Conference

CLINICAL CONFERENCE, ST. LOUIS CHILDREN'S HOSPITAL

Case 1. Hypereosinophilia With Eosinophilic Granuloma of the Liver Associated With Ascaris Infestation

DR. M. REMSEN BEHRER (Resident).—R. F. B., a 15½-month-old white boy, was admitted to the St. Louis Children's Hospital on Sept. 30, 1950. Two months prior to admission he was found to have temperature of 104° F. which continued in a remittent fashion with afternoon rises. After several days, he was seen by a doctor who administered intramuscular penicillin once a day for four days. When the temperature failed to respond to this treatment, he was hospitalized and given 60,000 units of penicillin every three hours. Four of six blood cultures grew out an organism believed to be a pneumococcus. When the child failed to respond to penicillin, he was given aureomycin for five days along with penicillin and then changed to Chloromycetin and aureomycin. Although there had been no meningeal signs during this period, a lumbar puncture was performed; the fluid was clear but contained 20 cells. At that time the child's peripheral blood showed a mild hypochromic anemia and a leucocytosis varying between 30,000 and 40,000 with a mild left shift. X-rays of the chest revealed a minimal bronchopneumonia. During this period of time, despite the high fever, the child did not appear ill and continued to be playful. Re-evaluation of the case in August revealed some prominence of the mastoid emissary vein on the left, a mucopurulent nasal discharge, a grade 1 systolic murmur along the left sternal border without transmission, and enlargement of the liver to two and one-half finger-breadths below the costal margin. The spleen was not palpable. Despite all studies, such as repeated lumbar puncture, negative tuberculin intradermal skin test, repeated urinalyses, and full coverage with streptomycin, penicillin, and triple sulfa mixture, he continued to have fever and hepatomegaly without apparent cause and without amelioration. Repeated stool examinations for ova and parasites, and stool cultures, were negative. In August, 1950, the child developed an eosinophilia of 20 to 53 per cent, a bone marrow study was made with notable findings, and cultures for histoplasmosis proved negative. Agglutinations for undulant fever and tularemia were negative. Since there was no response to drug therapy, all chemotherapeutic agents and antibiotics were discontinued, and the patient was referred to the St. Louis Children's Hospital for further study.

The past history revealed that he was born after eight and one-half months' gestation, during the latter part of which the mother developed signs of toxemia of pregnancy. Birth weight was 5 pounds, 4 ounces. Delivery was uneventful. After birth,

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the child responded well and subsequently developed normally. He received immunizations for diphtheria, pertussis, tetanus, and smallpox. He continued to be perfectly well except for a mild case of diarrhea at 11 months of age, measles at 12 months, and an occasional upper respiratory infection.

Fig. 1.—Diffusely nodular liver at the time of operation.

The family lived on a farm but drank only pasteurized milk and city water. The family history was negative. Physical examination on admission revealed a well-developed, well-nourished white male with a temperature of 38.8° C. Respirations were 22 per minute, the pulse 90 per minute. The boy did not appear acutely ill but was very irritable. The skin was warm and moist. There was a port-wine, arterial hemangioma on the left ear lobe. The neck was supple. Examination of the ears revealed a postmyringotomy perforation in the left drum in the superior-posterior quadrant without drainage. The right ear drum was normal. The pharynx was moderately red with moderate enlargement of the tonsils. The lungs were clear to auscultation and percussion. The heart was of normal size; its sounds were of good quality, and no murmurs were heard. Examination of the abdomen revealed the liver to be 1 cm. below the costal margin, but the spleen was not palpable. The genitalia and extremities were normal. Neurological examination failed to reveal any abnormal findings.

Laboratory studies revealed a hemoglobin of 12.2 Gm. per cent with 4.22 million red blood cells and 55,900 white blood cells. Platelets seemed adequate. The differential white blood cell count revealed 50 eosinophiles, 16 segmented, 28 lymphocytes, and 6 monocytes. Repeated counts later were similar. Uri-

Fig. 2.

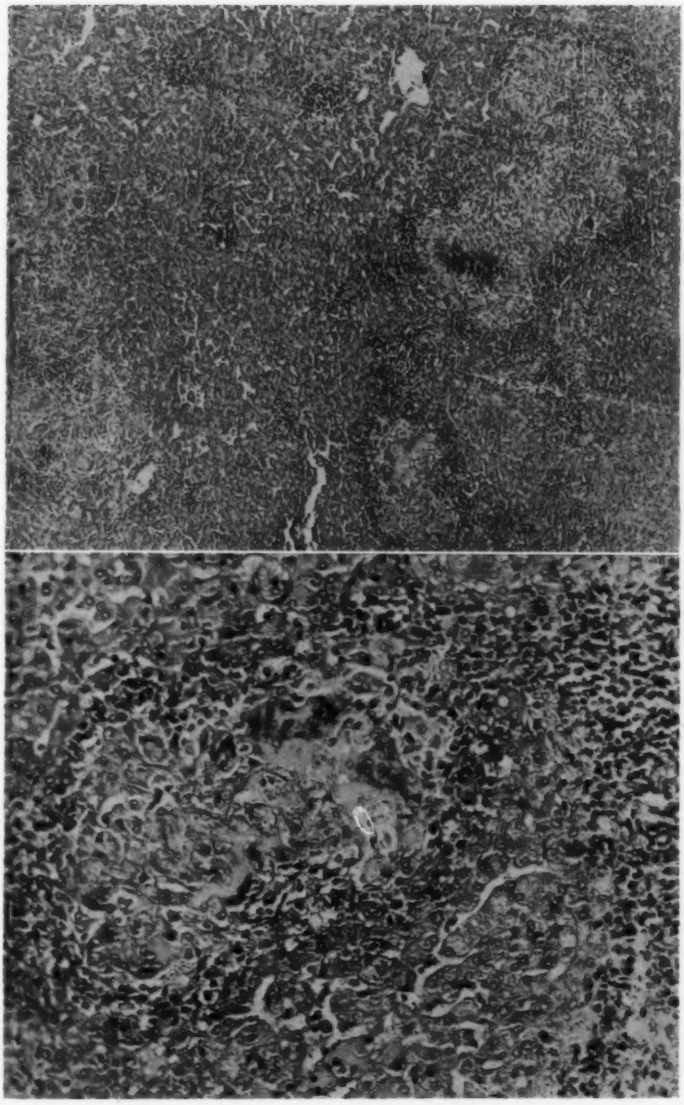


Fig. 3.

Fig. 2.—Section of liver showing eosinophilic granulomatous reactions of varying ages occurring in portal spaces (low power, hematoxylin and eosin stain).

Fig. 3.—Section of liver showing a granuloma with giant cells, fibroblastic proliferation and intense infiltration with eosinophilic leucocytes (high power).

nalyses were negative except for a slight trace of albumin in one sample. The intradermal tuberculin and the Kahn tests were negative. Lumbar puncture revealed clear fluid with 30 cells, 90 per cent polymorphonuclears. Culture was sterile, and chemical examination revealed 27.2 mg. per cent sugar and 55.5 mg. per cent protein. Blood chemical studies revealed a serum protein of 9.70 Gm. per cent with an albumin of 2.78 Gm. per cent, globulin 6.92 Gm. per cent. Agglutination tests were negative for brucellosis and typhoid. Cephalin flocculation test was 3+ in forty-eight hours. Blood cultures were sterile. Stool examination revealed ova of the *Ascaris lumbricoides* in one out of three samples. Following admission, a bone marrow study was done which revealed normal erythroid and megakaryocyte elements. The myeloid elements showed uniform eosinophilic hyperplasia. X-rays of the chest on Oct. 2, 1950, revealed the lungs to be clear and the heart of normal size and configuration. X-rays of the mastoids revealed some haziness of the air cells on the right side; however, the trabeculi appeared to be intact. This was interpreted as suggestive of acute mastoiditis on the right. A trichinella skin test performed at this time was negative. Oct. 3, 1950, an exploratory laparotomy was performed by Dr. Peter Heinbecker. The liver was diffusely nodular, the nodules being yellow-white and slightly raised and measured from about 0.5 to 3 mm. (Fig. 1). A few enlarged lymph nodes were noted in the mesentery of the larger and small bowel. A small biopsy of the liver was taken with specimens for culture for bacteria and fungi. These cultures subsequently grew nothing.

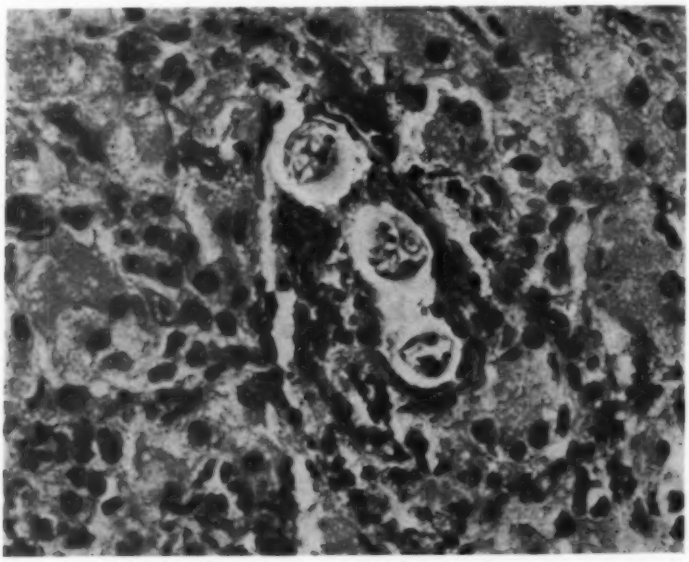


Fig. 3A.—Larvae of *Ascaris lumbricoides* in the liver (high power).

The pathological report by Dr. Lauren Ackerman on the gross specimen revealed a triangular section of liver with small whitish areas spread throughout. Microscopic examination of the specimen revealed a patchy infiltration with eosinophiles, associated with a granulomatous reaction (Figs. 2 and 3). Numerous giant cells were present. The sections were kindly reviewed by Dr. H. Z. Lund who found the larvae of *Ascaris lumbricoides* as seen in Fig. 3*A*. This finding was accepted by both Dr. Lauren V. Ackerman and Dr. H. Tsuchiya when they restudied the sections. The impression was a granulomatous reaction with diffuse eosinophilic infiltration. A repeat bone marrow examination revealed hyperplasia of the eosinophilic elements with normal maturation. During hospitalization, the parents' blood was examined, and neither one exhibited any increase in white blood cells or in eosinophiles. Following surgery, the patient was put on Hetrazan, 50 mg. t.i.d., and discharged on Oct. 12, 1950.

DISCUSSION

DR. W. G. KLINGBERG.—This infant, in summary, had a prolonged febrile illness with minimal significant findings initially and without response to the various drugs and antibiotics used. It seemed to be an infectious illness, at least early in the course as indicated by fever, leucocytosis, and demonstrated bacteremia. It seems very peculiar, however, that the organism initially cultured from several blood cultures and thought to be a pneumococcus was apparently not sensitive to the antibiotics in vivo, and yet that is the one organism that has seemed to be the most constantly sensitive particularly to penicillin. Such diseases as mastoiditis with lateral sinus thrombosis or other foci that might give rise to recurrent bacteremia could not be substantiated. It was not until after several weeks of his disease that a characteristic clinical syndrome developed. This syndrome of hyperleucocytosis, hypereosinophilia, hyperglobulinemia, and eosinophilic granulomatous lesions of the liver has been described recently in several papers.[1-3] Since these papers were published, this is the second proved case we have observed in this hospital.

When known diseases causing hypereosinophilia, such as trichinosis, polyarteritis nodosa, extreme allergic states, and eosinophilic leucemia can be ruled out, one is left with an obscure group of disorders reported under various names as chronic eosinophilia, eosinophilia leucemoides, Loeffler's syndrome, and others. Some instances of familial eosinophilia probably belong in this same category. The papers mentioned[1-3] have done much to clarify the problem and at least to indicate that they may be grouped together into one syndrome. One is impressed by the age incidence of the group of patients thus far reported with this syndrome. They have all been between 18 months and 3 years of age. This patient was 15 months of age. The vast literature of Loeffler's syndrome would indicate that older children and young adults are commonly affected. It would seem, however, as though hepatic involvement were a feature more common in early childhood than in later life and suggests that the liver may function as the main "shock organ" in the younger patients. By the same token, hyperleucocytosis seems to be more common and to reach higher degrees

in children than in adults. Some cases with leucocyte counts of 100,000 have been reported.

In all the cases reported where liver sections have been described, the pathologic process seems to be the same in all. The essential histopathologic features are those of granulomatous lesions primarily in the portal tracts which are intensely infiltrated with eosinophilic leucocytes. These granulomas in this case and in others vary in apparent age of the lesions in the same section. Areas of focal necrosis, giant cell and fibroblastic reaction, complete healing with fibrosis and calcification may be seen. Our own patient did not show healed lesions. The presence of lesions of varying ages indicates a cyclic recurrent nature of the pathologic process, and this is substantiated by the history in these patients.

As regards etiology of this syndrome, much confusion exists. Most authors express the feeling that the process is probably on an allergic-hyperergic basis. This point of view is strengthened in the descriptions of the disorders previously mentioned and also in the younger children with liver involvement by the frequency of widespread so-called allergic manifestations. These are asthma, urticaria, purpura, joint swelling, and in patients with Loeffler's syndrome, transitory pulmonary infiltrations and eosinophilia. In the papers of Perlingiero[1] and György and Mercer and associates,[3] they stress the possibility of hyperergic reaction to ascaris larvae or their products as the causative factor with the liver being the main shock organ in small children. Zuelzer and Apt's[2] cases failed to show any evidence of ascariasis either in the stool, liver, or by skin test. However, Mercer and collaborators did demonstrate ascaris larvae in the liver sections of their case, as was also seen in our case. A variety of other agents have been incriminated in all of these disorders, such as pollens, bacterial infections, drugs, mites, *Ancylostoma braziliense*, and many others. It seems probable that a number of agents may cause these disorders and that the basis of the manifestations is allergic in nature.

As to the significance of ascaris infestation in the production of this syndrome, several interesting things may be mentioned. It has been shown that the keratin from *Ascaris suis* is a powerful eosinophilotactic agent. Also, in the experimental studies of Kerr[4] it has been shown that during the initial infection of guinea pigs by *A. suis* there was only slight tissue response to larvae, whereas repeated infections produced a marked granulomatous response similar to that described in this patient and in this syndrome. In view of these facts, it would seem that while ascaris may not be the only etiological agent capable of producing visceral lesions and hypereosinophilia, it certainly seems to be capable in some instances. Probably the mechanism is an allergic one and may be produced by the presence of antigen-producing larvae within the liver or lungs or other organs and the hyperergic tissue response to this antigen.

The ultimate prognosis seems to be good. Specific antiascaris therapy should be administered when evidence of a s c a r i a s i s exists. Antiallergic therapy seems also to be indicated, particularly with the antihistamines.

Case 2. Jejunal Polyposis With Intussusception and Melanin Spots

DR. M. REMSEN BEHRER (Resident).—C. W., a 14-year-old boy, was admitted to the St. Louis Children's Hospital on Oct. 4, 1950, because of bloody bowel movements of two and one-half days' duration. He had been well until four or five years previously when he began having attacks of cramping abdominal pain which would usually last ten or fifteen minutes and followed the ingestion of fried or highly spiced foods. The pain was referred to both right and left upper quadrants of the abdomen and seemed sometimes to be relieved by vomiting. After the child's mother avoided giving foods which seemed to bring on these attacks, the episodes were reduced in frequency to one every month or two. When experiencing an attack in December, 1949, in addition to the cramping pain he complained also of a ball rolling back and forth from right to left in his upper abdomen. Five to ten minutes later he vomited and had complete relief. Similar attacks recurred about every four or five hours and were also relieved by vomiting. After several days of symptomatic treatment by the family physician, all symptoms disappeared, but because of anemia, treatment with liver extract and iron was given. The next severe attack occurred in August, 1950, following which, two days later, he passed a well-formed black tarry stool. Stools were then again normal, and he seemed well until four days prior to admission when he suffered recurrence of intermittent crampy pain and vomiting for two days. Following this episode he remained very listless, passed a stool containing bright red blood, and was found to have some fever.

Later, more detailed history revealed that the family lived in a rural area with no sanitary conveniences, and, therefore, examination of the stools was possible only when the patient was ill and used a bedpan. The vomitus apparently never contained fresh or old blood, nor had bleeding occurred from any site other than the intestinal tract. No jaundice was ever noted, but pallor had been present for four or five years, becoming particularly noticeable during the few weeks just prior to admission.

The patient's past history was essentially negative except for the usual childhood diseases and a short attack of jaundice at the age of 4 years.

The family history revealed that the remainder of the family—the mother, father, and five siblings—were all well and had never experienced attacks similar to the patient's. Later questioning also failed to establish melanosis in any other members of the family.

Physical examination upon admission revealed a quiet, pale, anxious-looking white boy who seemed fairly well developed but poorly nourished. The lips were deep red in color, and there were a large number of very small, discrete, deeply pigmented areas covering the lips, cheeks, and buccal mucosa (Fig. 4). There were many similar lesions about the nose (Fig. 5). Blood pressure was 110/60; the pulse was 100, and the temperature was 38.1° C. There were several ecchymotic areas over the lower extremities. The fundi showed marked tortuosity of the vessels and looping of the vessels over the disc margins. Many teeth were carious. The heart rate was 100;

rhythm was regular and the tones of good quality. The PMI was in the fourth to fifth interspace about at the nipple line. There was a grade 2 medium-pitched systolic murmur heard best in the left second and third interspaces and transmitted near the apex. The abdomen was scaphoid, and the liver, spleen, and kidneys could not be palpated. There were no masses palpated. There was slight voluntary rigidity near the umbilicus with tenderness to palpation and percussion. Peristaltic sounds were normal. Examination of the extremities was negative except for slight pallor of the nail beds. Examination of the back revealed a scoliosis with kyphosis. There was slight cervical adenitis but no generalized adenopathy. Rectal examination revealed a red to deep brown-black stool. No masses were palpated. Sphincter tone was normal. There were, however, numerous external hemorrhoidal tags.

Laboratory examination upon admission revealed a hemoglobin of 7.4 Gm. per cent with 3.49 million red blood cells and 8,650 white blood cells with 4 eosinophiles, 2 stabs, 54 segmented, 35 lymphocytes, and 5 monocytes. Platelets were adequate. The red cells were hypochromic. Urinalysis was negative. The intradermal tuberculin and Kahn tests were negative. Stool examination for blood revealed a positive guaiac test. Stool cultures revealed no nonlactose fermenting organisms. Blood culture was sterile. Following admission, the patient was given a barium enema which was entirely normal.

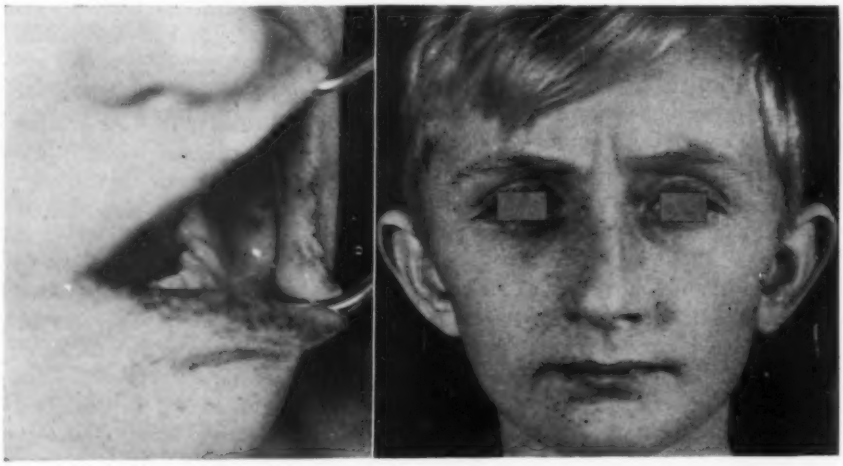


Fig. 4. Fig. 5.

Fig. 4.—Pigmented areas of lips and buccal mucosa.
Fig. 5.—Pigmented areas of face, particularly about mouth and nose.

DR. WAYNE A. SIMRIL.—Fluoroscopic and radiographic examination of the upper gastrointestinal tract following ingestion of a barium meal revealed a striking picture. The esophagus, stomach, and proximal duodenum were entirely normal in appearance. The second part of the duodenum, however,

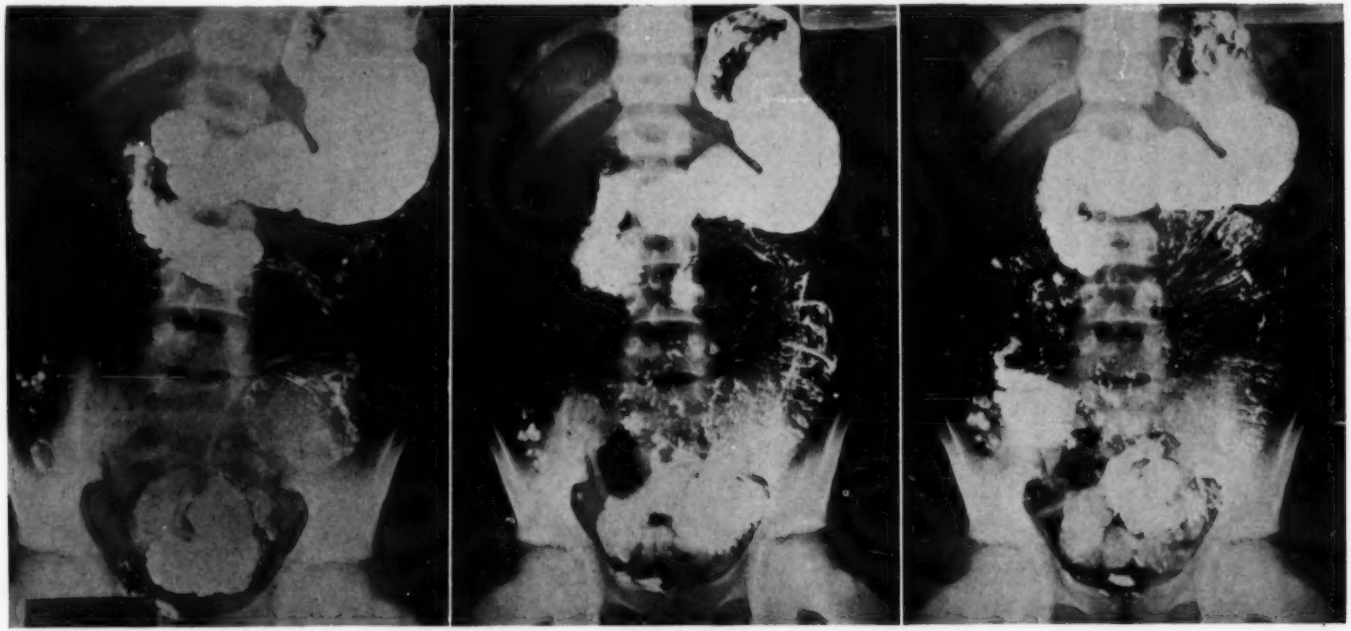


Fig. 6. Fig. 7 Fig. 8.

Fig. 6.—Film showing early appearance (fifteen minutes) of partial obstruction of duodenum and beginning formation of "stringlike" intussusceptum and "napkin-ring" or "sleeve" of the intussuscipiens.

Fig. 7.—Appearance at two hours of the well-formed intussusception.

Fig. 8.—Appearance at five hours; barium has reached the cecum in a normal time interval, but the grossly dilated intussuscipiens remains, and retention of perhaps 50 per cent of the barium meal in the stomach is noted.

was slightly dilated; and, at the junction of the second and third parts of the duodenum, a partial obstruction was noted (Fig. 6).

Enough of the contrast medium passed the obstruction to outline the invagination of a large portion of the proximal jejunum into adjacent jejunal loops. The formation of the intussusception is beautifully demonstrated in Figs. 6, 7, and 8. The "stringlike" appearance of the invaginated intestine, or intussusceptum, is best shown in Figs. 6 and 7. The "napkin-ring" or "coil of wire" appearance characteristic of the intussuscipiens is seen in Figs. 7 and 8.

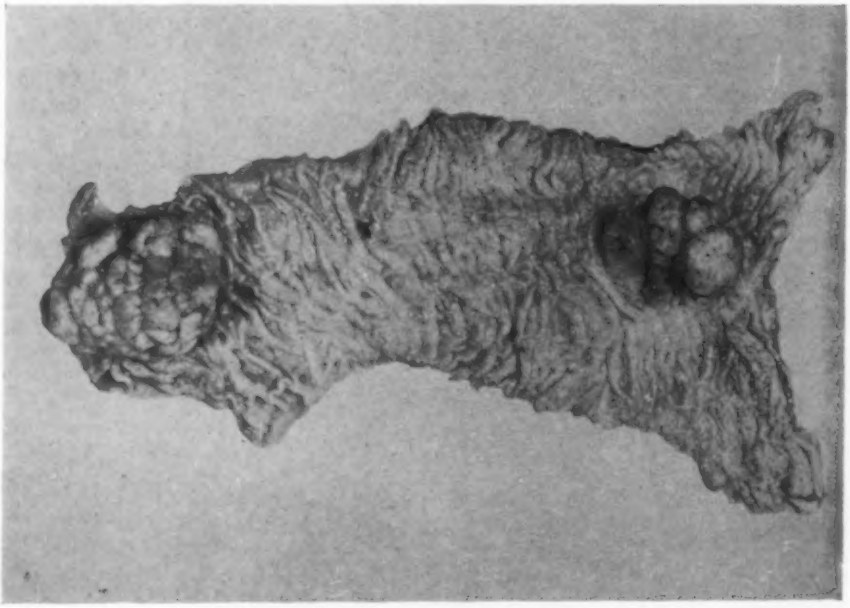


Fig. 9.—Twenty centimeter length of jejunum showing the two polypoid papillary adenomas.

The fluoroscopic and radiographic picture obtained in this case is sufficiently typical of intussusception anywhere in the gastrointestinal tract to allow for immediate and unequivocal diagnosis. This is true in spite of the fact that intussusception of any portion of the small intestine, except the terminal ileum, is an exceedingly rare lesion. Most radiologists never see such a lesion, and authorities such as Caffey, Hodges, Golden, and Feldman make no mention of jejunal intussusception in their publications.

The diagnosis of jejunal neoplasm as an initiating factor in the formation of this intussusception could also have been made with a fair degree of assurance. Intussusception in the absence of such a lesion is almost unheard of except in the ileocecal type which frequently occurs spontaneously in small children.

DR. M. REMSEN BEHRER.—On Oct. 15, 1950, the child was operated upon,

and at that time a large intussusception was found, about one and one-half feet in length. The intussuscipiens was seen to ring the intussusceptum approximately 10 cm. from the ligament of Treitz. It was reduced with gentle traction, and the bowel was found to be enlarged and edematous. The proximal portion of the intussusception could not be completely reduced, and upon further examination a large polyp was found. Palpation of the remaining small bowel revealed no evidence of any other polyps. An intestinal resection was performed; approximately 20 cm. of jejunum from the ligament of Treitz distally was excised, and the bowel was anastomosed. Examination of the polyps by the Pathology Department revealed them to be typical papillary adenomas (Fig. 9). Following the operation the patient had an uneventful recovery and during the following week gained about two pounds. The patient was discharged as cured, to be followed in the Out-Patient Department.

DISCUSSION

DR. W. G. KLINGBERG.—While the x-rays were beautifully diagnostic in this case, and there is little need for further elaborate discussion, it should be of interest to mention briefly a few of the diagnoses which were entertained in this child. I think that we all realized that this child had a serious illness because of his general appearance and that his recurrent abdominal pain was of real significance and not comparable to the vague abdominal complaints that so many children manifest without ever becoming seriously ill. A recurrently bleeding peptic ulcer first came to mind because of the epigastric pain. There was, however, no history of burning sensation, and the pain occurred within fifteen minutes after eating and was actually made worse by more food intake. With a peptic ulcer, one would expect the burning and pain to occur about an hour or two after meals and to be relieved by food. Furthermore, the patient had a phlegmatic personality and was not the jittery, high-strung individual so frequently seen with peptic ulcer. The history of tarry stools would indicate bleeding high in the intestinal tract, but the large amount of bright red blood would be very unusual in peptic ulcer unless the bleeding had been massive and rapid. His degree of anemia, while severe for his age, was not as severe as one would have expected if the bleeding were due to an ulcer. However, one of the reasons a gastrointestinal series was done was to rule in or out a peptic ulcer.

His history of recurrent bouts of acute pain, relieved by vomiting, and particularly the story that at least two episodes were followed by bloody bowel movements were quite suggestive of low-grade recurrent intestinal obstruction with intussusception. It is quite unusual to see intussusception in a child of this age, but it does occur. Typical pediatric intussusception occurs in infancy, usually in the second half of the first year and is characterized by signs of recurrent abdominal pain and the typical current-jelly bloody bowel movement. Certainly his pain and bloody movements were compatible with this diagnosis. We then felt that he might well have a malignancy of the intestine or associated with the intestine, such as a lymphoma or leiomyosarcoma, which could initiate the symptom complex and also lead

to the severe degree of malnutrition characteristic of malignancy. This type of lesion could lead to recurrent bouts of intestinal obstruction and particularly to severe anemia of the chronic blood-loss type. His bone marrow and peripheral blood were not characteristic of a generalized lymphoma.

The x-ray diagnosis of chronic intussusception was unequivocal, and then when Dr. Richard Lemmer confirmed it at operation and found that two polyps were the cause, we were both relieved and surprised. In retrospect, we should have made just that diagnosis on listening to the typical history and glancing at the child. In December, 1949, Jeghers, McKusick, and Katz[5] described a diagnostic syndrome of generalized intestinal polyposis and the occurrence of melanin spots of the oral mucosa, lips, and digits. The ten cases reported by them were comparable in every way with our present one and were characterized by symptoms referable to recurrent intussusception of the small intestine. By contrast, rectal or large bowel symptoms were minimal or absent. Most of the polyps were found in the small bowel, although in some cases they were also present in the stomach and large bowel. Our patient, as judged by palpation, had only the two polyps found in the small intestine. While we did not biopsy one of the melanin spots, those described by Jeghers and associates showed the deposition of melanin in the epidermis in vertical bands. There was no melanin deposition in the bowel in any case. They also felt that this syndrome had familial characteristics and appeared to be inherited as a simple Mendelian dominant. In our case, however, there was no apparent familial trend as the mother, father, and five siblings had no evidence of melanosis, nor had symptoms of intestinal obstruction occurred in any of them. Both males and females apparently carry the factor and are affected equally. All patients reported had had their melanin spots from infancy and had had episodes of abdominal pain in childhood.

Case 3. Mediastinal Emphysema, Pneumothorax, and Subcutaneous Emphysema Complicating Kerosene Poisoning

DR. M. REMSEN BEHRER.—G. D., a 12-month-old white male, was perfectly well until four days prior to admission to the St. Louis Children's Hospital on Nov. 29, 1950, at which time he drank a mouthful of kerosene. The child had a severe coughing paroxysm following the ingestion, and the breath had a distinct kerosene odor. He was immediately given water to drink, but shortly thereafter became unconscious and was taken to a local hospital where the stomach was lavaged with sodium bicarbonate solution through a rubber catheter. There was some uncertainty as to whether the tube was soft or stiff. During the procedure it was noted that the child was moderately cyanotic. After admission to this local hospital, he was given a coffee enema, oxygen per nasal tube, and started on Duracillin, 0.5 c.c. daily. About three and one-half hours after the ingestion of the kerosene, the child regained consciousness.

During the first day the child seemed to improve but remained very irritable and would not sleep. No fluids were offered by mouth. Later that evening the child's respirations became more

rapid. Within about twenty-four hours, it was noted that in addition to the rapid respirations the child had some intercostal and suprasternal retraction. At that time x-rays were taken which showed diffuse bilateral pulmonary infiltration, especially in the lower lobes. One day prior to admission here, a fullness of the neck was noted involving the anterior aspect of the chest and neck, and the respirations were more rapid and labored. The swelling of the neck extended to involve the shoulders, and on the day of admission an x-ray revealed bilateral diffuse pulmonary infiltration involving both lung fields and considerable mediastinal emphysema with posterior displacement of the heart. There was a large amount of air seen in the suprasternal area over the clavicles. A blood count done on the first day of the illness revealed a red blood cell count of 5.08 million, a hemoglobin of 14 Gm. per cent, and 5,400 white blood cells with 10 segmented, 88 lymphocytes, and 2 monocytes. Blood count taken prior to admission to the St. Louis Children's Hospital on the day of admission revealed a white blood cell count of 18,400 with 79 segmented, 1 eosinophile, and 20 lymphocytes.

The child's past history revealed a normal delivery with spontaneous respirations. Feeding history and developmental history were normal. Family history was essentially negative except for the fact that the father and a 3-year-old sibling suffered from asthma.

Physical examination upon admission revealed a critically ill, well-nourished, well-developed male child who would respond to stimuli and resisted oxygen per mask. The respirations were very labored and grunting in type. Temperature was 37.4° C.; pulse was 140 per minute, respirations 100 per minute, and blood pressure 130/84. Examination of the head revealed normal contours, with a circumference of 48.75 cm. The anterior fontanel was open but very small. The pupils were dilated but reacted to light. Examination of the ears revealed mildly injected tympanic membranes bilaterally. The nose was negative. Examination of the throat revealed mildly injected tonsils. The neck was supple but was markedly enlarged over the anterior aspect. Crepitation was elicited over the left side of the face involving the temporal region, the anterior portions of the neck extending out over the shoulders and down over the anterior portion of the chest. Examination of the lungs revealed a moderate limitation of motion on the right side. Breath sounds were distant bilaterally but more so on the left side. Chest was resonant to percussion throughout. There were no râles or rhonchi heard. The abdomen was flat and soft. The liver edge was felt at the level of the umbilicus but was not pulsating. The spleen and kidneys were not palpable. Examination of the back revealed some crepitation over the trapezius muscles. The skin turgor was fair. There was mild cyanosis of the nail beds and lips.

Immediately upon admission the child was put into oxygen and soon afterward was fluoroscoped. There was a marked infiltration throughout both lung fields and a questionable pneumothorax on the right. At that time a thoracentesis was done, but no air was found. After one-half to one hour in oxygen, the child's color and respirations improved somewhat. He was taken to x-ray and given a Lipio-

dol swallow in order to determine if any perforation of the esophagus had occurred. During this procedure, however, the child stopped breathing suddenly and became very cyanotic. Artificial respiration had to be instituted. It was noted at this time that the subcutaneous air in the neck and shoulders had greatly increased. The patient was laryngoscoped and an endotracheal tube introduced through which oxygen was given. Slowly, color improved, and the patient was taken to the operating room where a needle was inserted in the right anterior chest wall and about 50 c.c. of air under pressure were removed. At this time a tube was inserted in the right chest for closed pleural drainage, and an oblique incision was made over the right supraclavicular region, and the anterior mediastinum was entered. A moderate amount of air bubbled from the wound. A small Penrose drain was placed into the anterior mediastinum. The child was returned to the ward in fairly good condition.

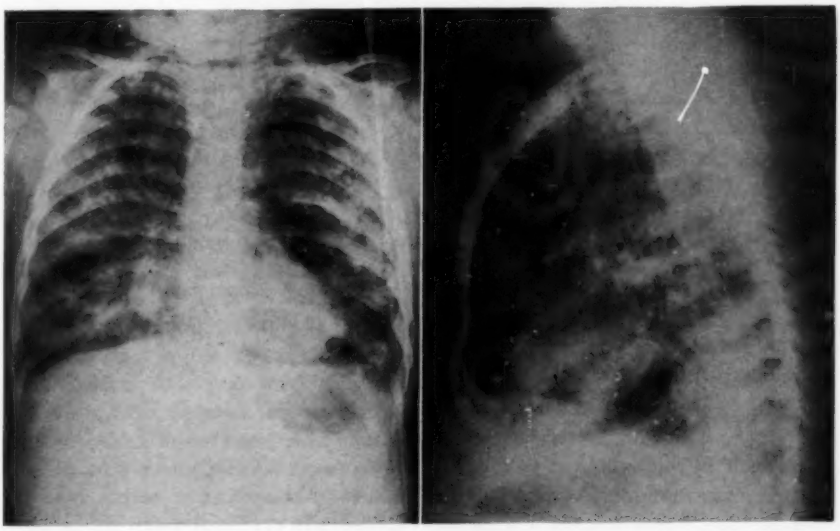
Laboratory work at this time revealed a hemoglobin of 12.3 Gm. per cent with 4.19 million red blood cells and 10,300 white blood cells. The differential revealed 4 stabs, 45 segmented, 51 lymphocytes. The urine was negative. The tuberculin and Kline tests were negative.

The next morning the child's color was still only fair, and respirations were still grunting. Breath sounds were well heard on the right side, but on the left side were distant, with wheezes and expiratory rhonchi. A chest film taken that day revealed a left pneumothorax, so a tube was placed into the left side of the chest for closed pleural drainage.

During this time the child received supportive therapy of parenteral fluids and was placed on streptomycin, penicillin, and intravenous terramycin. On the third day of hospitalization the child developed a temperature of 39.5° C. Examination revealed the breath sounds to be coming through bilaterally, and the tubes from the chest were not oscillating. The child's condition slowly improved, and on the fourth day of hospitalization the patient's temperature was normal. On the fifth day the child was fluoroscoped, and no evidence of pneumothorax was found on either side. Mediastinal emphysema was markedly reduced. Oxygen was discontinued, and the thoracotomy tubes were removed. On the sixth day of hospitalization, the patient was started on oral fluids which he took fairly well. His subsequent recovery was complete and uneventful, and he was discharged on Dec. 23, 1950.

DR. WAYNE A. SIMRIL.—The roentgenographic findings in this case are typical of chemical (and particularly kerosene) pneumonitis. The flocculent "soft" infiltrations scattered throughout both lung fields are indicative of a widespread reaction of the lung parenchyma to a toxic substance. The greater density of the lesions in the basilar portions of the lungs is accounted for by the almost inevitable aspiration of at least part of the ingested material by the small children who are the chief victims of this type of poisoning (Fig. 10). Lesser, Weens, and McKey[6] state that this is the sole mechanism. In my opinion, lesions in the periphery and apices of the lungs are the result of an edematous reaction in the alveoli and lesser bronchioles to an actual excretion of the

Fig. 10.—Posteroanterior film two days after ingestion of kerosene—widespread interstitial and flocculent infiltration most marked in the bases. Early signs of mediastinal emphysema are present.



A. *B.*

Fig. 11.—*A*, Posteroanterior film two days later showing marked advance in degree of severity of parenchymal and mediastinal lesions. Massive subcutaneous emphysema has developed. Pneumothorax is present bilaterally. *B*, Lateral film of the same date showing marked retrodisplacement of the heart and great vessels by air in the anterior mediastinal tissues.

more volatile fractions of the kerosene via the lungs.

The roentgenographic appearance of the mediastinal emphysema (Fig. 11*A* and *B*) in this case differs in no way from the more common traumatic type. Since the preliminary stage of pulmonary interstitial emphysema, which results from rupture of the alveolar bases into the perivascular tissues (Macklin and Macklin[7]), is not visible in x-ray films, the diagnosis of this specific type of mediastinal emphysema rests on history and physical findings.

The roentgen diagnosis in severe cases such as this is easy. In less advanced cases the only x-ray finding may be a few fine streaks of diminished density along the borders of the heart and/or in the perivascular and peritracheal areolar tissue. Not a few such cases are seen in retrospect after more striking findings are noted later.

A similar case has been reported by E. P. Scott[8] in a 2-year-old child. This patient, as in the case presented here, developed mediastinal and subcutaneous emphysema involving the face, neck, thorax, and upper abdomen. In addition there was a bilateral pneumothorax. Recovery was complete in twelve days.

Fig. 12.—Posteroanterior film three weeks after onset of the illness. No subcutaneous or mediastinal emphysema remains. The lung parenchyma has cleared almost completely.

DISCUSSION

DR. W. G. KLINGBERG.—Kerosene poisoning is one of the most frequent types of poisoning seen in pediatrics. Wherever kerosene stoves are still in use or wherever the oil is used to start open wood fires, it seems that parents are forever leaving it within reach of children in the toddler-age group. And to make it worse, the kerosene is usually kept in "coke bottles" or other soda bottles, making it more likely that the children will sample what to them will be "sody-pop." Following inges-

tion of kerosene, almost all of the children will choke, gag, cough, and vomit. Such symptoms are usually followed fairly quickly by drowsiness and lethargy which may progress to semicoma and even convulsions. Recovery may then ensue without further complications. However, at least 50 per cent of the cases will be complicated by clinical pneumonitis, and in cases reported where routine chest films have been taken, about 75 per cent will show x-ray evidence of pneumonitis. This complication is manifested by fever, rapid and usually grunting respirations, and the usual physical signs of bronchopneumonia. In the course of about one to two weeks, the process subsides with complete recovery. During this phase we feel it most important to treat them with supportive oxygen therapy and antibiotics to minimize secondary bacterial pneumonia, if possible.

The occurrence of mediastinal emphysema, subcutaneous emphysema, and pneumothorax in kerosene poisoning is a rare one, but a very real one. We have not seen it previously in our experience here or at the St. Louis City Hospital, and we usually see twelve to fifteen cases a year. It has been reported several times[6, 8] in the literature. Undoubtedly, it occurs more frequently than reports would indicate either from failure of recognition or failure to report the cases. Dr. Louis R. McFarland, one of our house staff, saw fifteen to twenty cases of kerosene poisoning a year in his own practice in rural Arkansas and remembers two cases complicated by subcutaneous emphysema and pneumothorax. The mechanism of the occurrence of mediastinal emphysema, subcutaneous emphysema, and pneumothorax in kerosene poisoning seems best explained by Macklin and Macklin.[7] In the experimental animal, the pneumonitis produced by kerosene injected into the trachea or intravenously is a focal, hemorrhagic inflammatory reaction in the alveoli. It is likely that the same type of reaction occurs in human beings, so that focal areas of pneumonitis and atelectasis are seen. Whenever this occurs, compensatory emphysema of uninvolved lung areas occurs and allows or initiates the development of mediastinal emphysema. According to Macklin and Macklin,[7] in the areas of compensatory emphysema the pressure gradient between the alveoli and their surrounding interstitial tissue is disturbed, so that the alveoli rupture, and air escapes into the interstitial tissue. This produces pulmonary interstitial emphysema. This air continues to collect and dissects upward along vessel branches to escape into the mediastinal tissues producing mediastinal emphysema. If the process continues, air eventually will rupture from the mediastinum into the pleural cavities, producing pneumothorax, or it will dissect up and down fascial planes to the subcutaneous tissue producing subcutaneous emphysema.

All of these processes were seen in this patient. Each produces further respiratory and circulatory embarrassment, and death sometimes results. Generally, when this type of pneumothorax occurs, the respiratory symptoms can usually be relieved by simple aspiration of the air as the pneumothorax is not a true tension pneumothorax and does not tend to recur. The mediastinal emphysema may also be aspirated, but because of its tendency to be multiloculated in the mediastinal

tissues, the relief of symptoms is not as thorough or dramatic. In this particular case it was initially felt that the mediastinal emphysema, subcutaneous emphysema, and pneumothorax might have resulted from esophageal trauma from the lavage tube. Because of the critical appearance of the child, closed tube intercostal drainage of the pneumothorax was carried out with prompt relief of symptoms.

DR. ALEXIS F. HARTMANN.—In many of our previous discussions of the problems presented by kerosene ingestion, the question was raised as to whether or not one should attempt to rid the stomach of as much kerosene as possible by gastric lavage. Bearing on this question is the known fact that pneumonitis may follow absorption of kerosene from the intestinal tract and its transportation to the lungs by the circulation (this, of course, would suggest that as much kerosene as possible be prevented from reaching the intestinal tract), by direct aspiration of the original kerosene, or by secondary aspiration during vomiting. Since the more volatile aromatic hydrocarbons of the mixtures constituting the kerosenes are more toxic than the less volatile aliphatic hydrocarbons, it has always seemed to me that consideration should be given to the vapor tension of the aromatic compounds as it would be influenced by temperature. It seems possible that some of the pneumonitis is the result of inhalation of volatilized hydrocarbon, especially during attempts at gastric lavage with warm solutions, and perhaps also after vomiting more inhalation of vapor takes place from the nose and pharynx.

I feel, however, that the stomach should be lavaged, preferably with cool saline solution and with the child's head in a dependent position and with a suction apparatus in operation to prevent not only aspiration of fluid but also inhalation of kerosene vapor.

It might also be interesting to comment further on the problem of mediastinal emphysema and pneumothorax. It is more common to encounter such complications after foreign body aspiration and obstruction in the respiratory tract and particularly after the performance of tracheotomy for the relief of high obstruction. The mediastinal emphysema and pneumothorax in this case of kerosene poisoning, I think, is quite similar in mechanism. On the other hand, the kind of pneumothorax that is encountered not infrequently in association with staphylococcal lung abscesses in infants is decidedly different in origin and in the treatment which is demanded. In this latter type there almost always occurs a bronchopleural fistula, so that a tension pneumothorax develops, and simple aspiration of the air accomplishes little because of the persistence of the bronchopleural fistula. Experience with such infants many years ago had convinced us that it was lifesaving to effect pleural tube drainage before fatal tension pneumothorax could develop. In this case of kerosene poisoning, as in most of the foreign body cases, one would not expect a bronchopleural fistula, and, on the other hand, one would expect that perhaps a single simple aspiration of the air would suffice; that is, there would not be extensive reaccumulation of air following aspiration.

However, I am not in any way criticising the handling of this case so far

as the surgical drainage of the pleural cavities and mediastinum is concerned. Such drainage was skillfully performed, and protection with antibiotics was given, and I think the procedure should probably be regarded as one more fully covering the more serious possibility of esophageal rupture as the cause of the mediastinal emphysema which, fortunately, had not occurred.

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Psychologic Aspects of Pediatrics

MOTHER-PEDIATRICIAN RELATIONSHIP IN THE NEONATAL PERIOD

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IDEAL pediatric care should begin before the birth of the child with advice to the mother concerning feeding and care of the baby, and guidance of the parents into proper emotional attitudes. Many problems such as the fear of inherited defects or diseases, bottle versus breast feeding, clothing and housing of the baby, management of sibling adjustments, and possible need of nursing and domestic help in the home, to name but a few, are best discussed before the arrival of the baby. These problems affect the baby as directly as the mother and are pediatric as well as obstetric responsibilities. Rarely, however, does the pediatrician see the mother until he is called to examine her new offspring.

Read[1] and Thomas[2] emphasized the psychologic importance of showing the mother her baby soon after delivery. She wants and deserves to see the product of her labors. If she is rational, the baby should be shown in the delivery room. Read stated: "That there is anything unsightly in the appearance of a newborn baby is nonsense; that a mother might be shocked by her own baby is fantastic."[1] Frequently the newborn infant is placed in a nursery for twelve or more hours until the feeding routine is started. The first visit to the new mother by the pediatrician, then, may be before she has seen the baby, and in this situation, she especially needs reassurance and a thorough report on the baby's anatomy, physiology, and apparent mental status. If she has already seen the baby, reassurance is still desired, and questions concerning real or imagined abnormal conditions may already have arisen.

If there are no abnormalities, it is well for the pediatrician to tell the mother that he has examined the baby "from head to toes" and that so far as one can tell everything seems normal. Further elaboration on the status of the heart and lungs, the anatomy of the hands, feet, and legs, the shape of the head, and the fact that the baby has already had a stool or urinated is considered valuable information by most mothers.

Examination of the newborn baby at the bedside of the mother, or on a sterile sheet on the bed itself, as advocated by Clifford,[3] is of especial value in pointing out deviations from the normal that are likely to cause worry. Such an arrangement as a routine, however, is often difficult because of the turmoil on obstetric floors, including meals, baths, perineal care, and visitors; moreover, the mother may still be under anesthesia

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when the pediatrician arrives for his examination. Nevertheless, every effort should be made actually to demonstrate abnormalities.

Pediatric attendance at delivery, especially when difficulty is anticipated, is becoming popular in some hospitals. This arrangement is not only advantageous to the baby, who thereby has his own attendant, but is valuable for the pediatrician in that he becomes aware of the infant's precarious entrance into the world and can observe his first reactions. The pediatrician can better interpret to the mother any morbid results of the delivery, and the mother-pediatrician relationship is thereby strengthened.

ABNORMALITIES AND DEVIATIONS

When to tell a new mother that her child has a congenital defect or disease is a practical problem of considerable magnitude. If the defect is obvious, such as a harelip or a clubfoot, if the disease produces obvious signs such as jaundice, or if frank cyanosis is present, the explanation is made, perforce, as soon as she has recovered from her labor. Many physicians, and I believe their number includes a great majority of obstetricians, think that a mother should be told frankly the nature and extent of all abnormalities as soon as feasible. If one considers the mother only, this plan may be best, but from the pediatric standpoint there are two beings to consider. Some emotionally immature mothers will create an unhealthy environment, especially with their first-born, if they know the infant has any sort of defect or deficiency. Unless especial care is needed, it might be better to spare the baby, for a few months at least, the overanxiety and overprotection that can play great havoc with proper rearing and enjoyment of children.

Kind deception for this minor group, until some adeptness in handling the baby has been secured, will not cause loss of faith in the doctor if it is explained that the deception was carried out for the best interest of the baby. One must not withhold information, however, without full knowledge and consent of the father (or of the mother's parents if he is not available), to whom a complete explanation must be given. His wishes, as well as those of the obstetrician, should be considered. Even in such major calamities as mongolism, the emotionally immature mother who must care for her child need not be told at once. In such a case, knowledge is withheld for the mother's sake, until she has recovered from the delivery and gained some degree of self-confidence. While separation of the mother and the hopelessly afflicted child at birth, as advocated by Aldrich,[4] is to be desired, the lack of placement facilities prevents this solution except in a few states and in the higher economic groups.

Brennemann,[5] who approached this problem mainly as a consultant, believed that, in the case of mongolism, having only one parent informed causes too great a mental burden and that knowledge of the abnormality should be shared. He stated, however, that when a child is mentally subnormal, it is probably best to let the parents gradually become aware of the defect, and that by showing more than usual interest in the child's development the family physician can implant a suspicion in

the minds of the parents that will make full realization, later, less of a shock. The pediatric consultant, on the other hand, must give an immediate opinion for the sake of the child, the parents, and his own reputation.

Some deviations, both in anatomy and physiology, are so common that they are not considered abnormal by the pediatrician, but may appear to be major calamities to the parents. If one considers such things as nevi, the curve of the fingers, and the shape of the ears and nose, it is obvious that almost every human being has some deviation from the average. Reassurance about deviations is probably the pediatrician's most appreciated service to parents of newborn babies.

While anatomic deviations can usually be found and discussed at the pediatrician's first visit to the mother, most of the physiologic ones, whether real or fancied, occur in the first few days after the birth of the baby. As seen in Tables I and II, average mothers have four times as many complaints or questions concerning physiologic problems as anatomic ones. The baby's first episode of regurgitation, sneezing, gagging, or coughing may be alarming to the inexperienced. If the pediatrician is to discuss such problems with the mother, daily visits are required. Reassurance and explanation from nursing personnel are often sufficient, but when the pediatrician delegates this duty to others, he runs the risk of erroneous information being given. He also misses an invaluable opportunity for establishing rapport with the mother and getting insight into her attitude toward the baby. Only brief visits are needed, and at each the mother should be given an opportunity to ask questions and express worries. Visits may be utilized for instruction in what to expect when the baby gets home, and

TABLE I. ANATOMIC COMPLAINTS MADE BY 100 MOTHERS OF NORMAL NEWBORN INFANTS

Eyes	
Crossed	1
Silver nitrate stain	1
Redness on lids	3
Shape of nose	3
Shape of mouth	1
Tongue-tied	1
Shape of ears	7
Breasts hard or swollen	2
Palpable xiphoid process	2
Cord	
Blue	1
Oozing	1
Bulging	1
Hernia	1
Crooked legs or feet	3
Skin too hairy	1
General	
Ugly	1
Too fat	3
Too thin	2
Total	35

TABLE II. PHYSIOLOGIC COMPLAINTS MADE BY 100 MOTHERS OF NORMAL NEWBORN INFANTS

Concerning eating and digestion	
Will not eat well	15
Hungry (not enough food)	15
Vomiting	19
Will not burp	5
Hiccough	2
Stools too loose	1
Draws up knees—"colic"	1
Eyes	
Discharge	10
Swollen lids	8
Will not focus	2
Nasal congestion	12
Sneezing	4
Gagging or choking (not associated with eating)	4
Does not cry; too sleepy	15
Too lively or tense	3
Skin	
Rash (heat, hives, "milk" rash)	18
Dry	2
Scratches	3
Jaundice	1
Loss of weight	2
Penis sore	1
Total	143

will, in most cases, save the mother many hours of worry and the physician innumerable telephone calls.

For several years I have kept a list of complaints and questions presented by over 500 mothers of newborn infants. In the series of 100 cases analyzed with regard to this feature in Tables I and II, premature and abnormal babies, and babies whose mothers had obstetric morbidity were excluded. In these cases from private practice the mothers' social and economic background was average. A great majority of the mothers stayed in the hospital five days post partum, and none less than three or more than nine days. In all cases a report on the baby was made at the original visit, and both the mother and the baby were seen every day. Care was taken to allow the mother to express concern or ask questions about her baby at each visit.

Fifty-seven of the mothers were multiparas and forty-three primiparas. Thirteen women had no questions nor complaints about their babies during the hospital stay, and of these, six were multiparas and seven primiparas. The fifty-seven multiparas offered ninety-one complaints, and the forty-three primiparas, ninety-four. In this group one may conclude that parity had little influence on anxiety or questions expressed by mothers of newborn infants.

Doubtless, the worries mothers have about their newborn infants are innumerable. The usual ones are included in Tables I and II. During the first day or two post partum, the head and its various organs are most commonly mentioned. Throughout the period of hospitalization the status of the eyes is a common concern. In my experience, however, few have curiosity concerning vision, and, furthermore, questions about ability to hear, taste, smell, or feel are unusual. As would be expected, eating and digestive behavior concern a mother most, since except in unusual circumstances, as with a rooming-in arrangement, the mother's only duty toward the infant is feeding. Hemangiomas are not listed in the table. This omission is due to the fact that they were discussed during the first report to the mother. Certainly, birthmarks, commonly seen in the area of the eyes, glabella, brow, or base of the skull, alarm the mother, and reassurances concerning them should be offered.

UNDERSTANDING THE NEW MOTHER

To explain fully the psychology of motherhood would involve the unraveling of the emotional and physical life of womankind. Deutsch[6] observed: "There are as many variations in the psychology of motherhood as there are mothers." Nevertheless, some fairly constant reactions to the reproductive process help one understand the new mother. There is value, moreover, in describing "pure" types of reactions even though in practice there is often a confusion of emotions and attitudes. If one understands the exaggerated reactions, more subtle variations become easier to recognize. The fascinating psychoanalytic aspects of motherhood, admittedly of importance, will be sacrificed here for a more superficial, and perhaps more practical, approach.

Fear is a normal accompaniment of the reproductive process. Fundamentally it is probably a fear of death. It may not, however, be recognized as such by the mother, who more often expresses fear of pain or fear for the child. Indeed, a large number of new mothers will deny having had any fears if questioned during the post-partum period. Fear may be forgotten, unrecognized, or denied through false pride. Recently popularized methods of obstetric management which attempt to eliminate fear through education of the expectant mother in the normal mechanics of having a baby cannot be expected to be wholly successful in abolishing this emotion. Women physicians, mothers themselves, who have delivered babies, will usually recognize and readily admit experiencing it in connection with having their own babies. Fear, especially if of great intensity, may be transferred to the baby in the form of anxiety.

Along with fear are varying degrees of joyful anticipation. In reproduction, the woman attains the ultimate expression of her biologic role, and even when the child is unwanted, there is a pride of accomplishment. Rationalization of the fear of childbirth, the only process in the human experience that is accompanied by severe pain and bleeding and nevertheless considered a physiologic phenomenon, is accomplished by joyful anticipation and pride. The presence of joyful anticipation is more variable than the presence of fear and is influenced by many situational factors, such as the attitude of the husband and friends, the economic status of the family, the mother's ambitions outside the home, and the number, discomfort, and recency of previous pregnancies. Joyful anticipation is often tempered by a dread of increased responsibility and work, but fortunately the drudgery connected with the care of the baby usually is not an important influence on the attitude of the new mother toward the baby.

Maternal attitudes toward a new baby are often confused, and, as pointed out by Bakwin and Bakwin,[7] attitudes of parents, whatever the age of the child, often are not permanent. This instability of emotional attitude is especially true of the woman in the post-partum period. Her emotions concerning the baby may vary from day to day and even from hour to hour. A not uncommon, dramatic example is the unwed mother who vigorously rejects her child until a few days before leaving the hospital, when she has a complete reversal of attitude, and subsequently becomes an adequate mother. Basing his opinion on attitudes and behavior during the lying-in period, the experienced physician can predict with a considerable degree of accuracy what kind of mother the parturient will become, but as with first impressions in general, one may be greatly mistaken. An open mind is certainly the wise policy.

Cooke[8] offered a psychologic classification of American mothers for obstetricians. Excluding the definitely pathologic, he described three prototypes. Of these, the most common, fortunately, is the emotionally mature woman who has been taught independence. He considered women of this type, "particularly if they have

been obliged to make or contribute to their own living," to be the most stable psychologically. He regarded the worst of the three the mother who sublimates herself in her daughter (a practice which could apply to sons as well), depriving the child of all unpleasant experiences in life and thereby preventing the attainment of emotional maturity. The child of such a mother, through no fault of her own, grows up unable to cope with the simplest problems, and "the psychologic anguish and terror of such a woman confronted by labor, when she discovers that neither her husband nor her mother can have her baby for her, is pitiable." The third type, although smallest in numbers, he feared is on the increase. "This type is not a mother at all: her total egocentrism ejects her unwanted child from her at the earliest possible moment." In type two one recognizes overt overprotection and in type three overt rejection without compensation.

In most social groups, pregnancy is regarded as a highly desirable and interesting state. Solicitude and attention enjoyed by the pregnant woman come to an end, to some extent, with delivery, and the baby becomes the focus of attention. Rejection of the infant, consciously or subconsciously, may result, the extent being almost directly proportional to the emotional maturity of the mother. Whenever rejection occurs on the conscious level, it may be associated with overprotection and anxiety, and it may be almost impossible to reassure a new mother with such an aberrant attitude. Deutsch[6] was of the opinion that it "is quite possible that in all anxious mothers repressed hostility toward the child plays a part." The pediatrician may try to offer insight, but his efforts will fail unless unusual rapport exists between him and the mother.

On the other hand, overaffection, overanxiety, and overprotection, unassociated with overcompensation from rejection, may occur, especially in the mother who has had a long unfulfilled desire for a child. Mothers of this type are usually cooperative, although often too literal, and may be guided into ideal motherhood. Prevention of transference of a mother's fear and overanxiety during pregnancy to the unborn child should be attempted during the months of pregnancy by the obstetrician or his consultant. After delivery, pediatric guidance is extremely helpful.

Psychiatrists are now fairly well agreed that there is no such entity as a puerperal psychosis, according to Cohen.[9] Pregnancy acts as a precipitating factor, however, and Piker[10] stated that 9 per cent of all psychoses in women are precipitated by the birth process. Apart from the manic states, which are usually brief reactions often associated with anesthesia, the types nearly always observed are schizophrenia and manic-depressive psychosis. The psychosis may provoke suicide or infanticide. Since the onset of the psychoses precipitated by reproduction is usually between the first and fourteenth day post partum, they may occasionally be encountered by the pediatrician, and although their management will not directly concern him, the possibility of their occurrence should not be overlooked. Decided changes in personality and attitude are the danger signals.

SUMMARY

The role of the pediatrician in the neonatal period is discussed, and the problems incident to abnormalities and deviations in the newborn infant are presented. Analysis of the complaints and questions of the mothers regarding their offspring in a series of 100 cases is reported; average mothers were four times as interested in physiologic as in anatomic problems. The relatively constant psychologic reactions to the reproductive process are reviewed as a key to the pediatrician's understanding of the new mother and as a guide to clarification of confused emotions and attitudes.

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Comments on Current Literature

RETROLENTAL FIBROPLASIA

THE January, 1951, issue of the *American Journal of Ophthalmology* carries an extensive article by Algernon B. Reese and Frederick C. Blodi[1] in which infant blindness is discussed. This article is, in printed form, the Fifth Francis I. Proctor Lecture in Ophthalmology presented by Dr. Reese at the University of California Medical School in September, 1950.

Retrolental fibroplasia, an important cause of blindness in infancy, is described by these authors as a "clear-cut entity affecting primarily premature infants of low birth weights. . . . The disease has an acute or active phase which subsides at about three months of age, and a late or cicatricial stage which follows thereafter. Characteristically the condition is bilateral. . . ." The acute phase is described as clinically recognizable between the third and fifth weeks of life, being characterized by dilatation of the retinal vessels, hemorrhage, neovascularization over the surface of the retina and vitreous, and transudation. The authors emphasize that spontaneous regression may occur during the early stages of the pathologic process but that when the stage of neovascularization and transudation is reached, spontaneous regression is rare.

Other, less common, causes of blindness in the young infant include persistent hyperplastic vitreous and retinal dysplasia. The former condition is associated usually with a persistent hyaloid artery, tends to be unilateral, and is characterized by the presence of opaque tissue behind the lens, which is more dense in the central portion. The latter condition, retinal dysplasia, is bilateral, is associated with some degree of microphthalmos, and is often associated with malformation elsewhere in the affected infant.

Before the cicatricial stage is reached the diagnosis of retrolental fibroplasia may be missed readily by the clinician. In consequence, this late stage which is irreversible and accompanied by serious loss of vision has come to be regarded erroneously by some observers as the typical manifestation in all cases of retrolental fibroplasia. Reese and Blodi point out that many cases of retrolental fibroplasia are known to occur which never progress to this final stage of organization and contracture. The authors illustrate their account of the disease by presenting the pathologic findings in the case of an infant with retrolental fibroplasia who died at the age of 11 weeks. The twin sibling of this child, who survived, is now totally blind and presents in both eyes the late cicatricial changes characteristic of retrolental fibroplasia.

The microscopic findings of the acute stage of retrolental fibroplasia are presented in detail, and are well illustrated by excellent photomicrographs. The angioplastic process in the vitreous, which consists of angiomatous tissue extending from the retina into the vitreous, is considered by the authors as characteristic of the pathologic state in retrolental fibroplasia. The presence of a hemangioma in the right orbit of this patient and of others in various parts of the body, particularly over the region of the head, suggests a relationship between the angioplastic process in the eye and the occurrence of hemangiomas in other parts of the body.

With this conception in mind the authors point out that skin hemangiomas occur in 1 to 2 per cent of all full-term infants, and in 3 to 10 per cent of premature infants. Their own experience indicates that 15 per cent of infants with retrolental fibroplasia have skin hemangiomas. It is stated further that only 17 to 20 per cent of the cutaneous hemangiomas are apparent in newborn infants at birth, and that 80 to 83 per cent become evident between the first and sixth weeks of postnatal life. On the basis of these observations the authors express the opinion that the "pathologic development of retrolental fibroplasia is that of an angiomatous process which manifests itself predominantly in the vitreous, and the many newly formed vascular channels are identical histologically with those associated with hemangioma" and that retrolental fibroplasia may represent a manifestation in the affected infant of a generalized angioplastic process.

In the section on therapy the authors stress the need for accurate diagnosis of the process during the active stage, prior to the time when irreversible changes have taken place, and point out that the results of surgical intervention in cases with late cicatricial changes have been disappointing.

Since January, 1950, Reese and Blodi have been collaborating with W. S. Silverman and R. L. Day of the New York Babies' Hospital, in an investigation of possible means of therapy. In view of their clinical observations and studies of the pathogenesis of retrolental fibroplasia, treatment of the acute phase with ACTH was undertaken. Since retrolental fibroplasia may be primarily a generalized disease of the blood vessels, and since hyperadrenalism inhibits the growth of mesenchymal cells and cortisone specifically inhibits the growth of capillaries, it seemed reasonable to this group of workers that ACTH might halt the vascular overgrowth which marks the beginning of retrolental fibroplasia.

The course of therapy used consists in the administration of 20 to 25 mg. of ACTH daily for a period of fourteen days. In two instances in which the disease process appeared to be reactivated after cessation of ACTH therapy, a second course of therapy was given. To date thirteen babies with early retrolental fibroplasia have been treated in this manner. In each instance the retrolental process was arrested, or has regressed. Of eight infants with progressive retrolental fibroplasia who, for one reason or another, did not receive ACTH therapy, three have complete bilateral membranes, three have partial membranes, and two have small masses of white tissue in the periphery of both fundi. On the basis of their limited experience to date, these workers are encouraged to continue the use of ACTH on an experimental basis. Used in the manner described no serious side effects of ACTH have been noted in any of the patients.

With the apparent increase in the incidence of infant blindness, many instances of which seem to be on the basis of retrolental fibroplasia, it is recommended that routine ophthalmoscopic examinations be made of all premature infants, especially those with low birth weights, and that such routine examinations be considered obligatory in all premature units. By careful study of these infants, early recognition of the disease process during the acute stage will be possible, and adequate therapy can be instituted before irrevocable changes occur.

RUSSELL J. BLATTNER.

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Correspondence

To the Editor:

In describing life in North Carolina in the 1820's when the Cotton Kingdom had brought African slaves to the Catawba Valley, Dr. Chalmers G. Davidson, Professor of History at Davidson College, N. C., stated that these Negroes believed that chicken pox in the pregnant mother might deform the unborn child.[1] One hundred twenty years later, Gregg, an Australian ophthalmologist, reported the damaging fetal effect of rubella during pregnancy.[2] During the next eight years, other virus diseases also have been found to have deleterious results during pregnancy.

Interestingly enough, several pediatricians with a wide knowledge of infectious diseases deny the Negro folklore that chicken pox in the mother will damage the fetus. However, Miller was able to collect the records of seven cases of chicken pox during the first four months of pregnancy and found that one of the infants had cataracts.[3] The paucity of this material probably is due to the fact that chicken pox is a rather uncommon disease in adults as compared with mumps and rubella.

Why has the medical profession been so slow in recognizing effects which Negroes had apparently known for generations? Probably because physicians do not practice observation as avidly as Osler recommended[4] and also because, as MacNider suggested, the observations frequently were not followed by a thoughtful "Why?"[5] Another reason that pediatricians do not know more about the effects of maternal diseases on children is the rigid separation of obstetrics and pediatrics by the specialty boards, and that too many pediatricians are still more interested in children's diseases than in child health. There should be a return to the old combined specialty of women and children. Pediatrics should be the care of children, in health and disease, both physical and mental, from conception through adolescence. The British policy of having Chairs of Child Health instead of Pediatrics, and the title of Grulee and Eley's book, *The Child in Health and Disease*,[6] are healthy signs.

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News and Notes

Dr. Katherine Bain, Director of the Division of Research in the Children's Bureau since 1940, has been appointed Associate Chief of the Bureau. She will take over responsibility in the maternal and child health field previously carried by Dr. Martha Eliot and more recently by Dr. Leona Baumgartner, in addition to the research program.

Dr. Bain was graduated from the Washington University School of Medicine in 1925 and after hospital training in the Children's Hospitals of San Francisco and St. Louis entered the practice of pediatrics in St. Louis. She was in active practice and on the teaching staff of the medical school from 1927 to 1940 when she entered government service. She is a member of the American Pediatric Society and American Academy of Pediatrics. She was certified in Pediatrics in 1943 and in Preventive Medicine and Public Health in 1949. From 1945 to 1947 Dr. Bain was a member of the staff of the American Academy of Pediatrics Study of Child Health Service.

The following were certified by the **American Board of Pediatrics** at the examination in New Orleans, La., March 2, 3, and 4, 1951.

Dr. Elaine Louise Allen, 1430 Tulane Ave., New Orleans, La.

Dr. Julia Baker, 2a Campos Eliseos 15, Mexico, D. F.

Dr. Donald Frederic Bauman, 404 Chapman Bldg., Fullerton, Calif.

Dr. Robert J. Black, Harbin Clinic, Rome, Ga.

Dr. Carl Arthur Brakel, 617-619 Fernwell Bldg., Spokane 8, Wash.

Dr. George R. Branch, 4325 Cole Ave., Dallas, Tex.

Dr. Daniel Wilbern Burke, Jr., 956 Dauphin St., Mobile, Ala.

Dr. Edwin C. Burklund, 1517 St. Clair, St. Paul 5, Minn.

Dr. Louise Holmes Burr, Permanente Hospital, 280 MacArthur Blvd., Oakland 11, Calif.

Dr. Donald E. Cassels, 920 E. 59th St., Chicago, Ill.

Dr. Lin Tung Chun, King Kalakaua Bldg., Room 217, 1415 Kalakaua Ave., Honolulu, Hawaii

Dr. Bernard I. Copple, Tokyo General Hospital, c/o Postmaster, San Francisco, Calif.

Dr. James Hewitt Cravens, 1101 Maine St., Quincy, Ill.

Dr. Robert Ralph Dew, 312 Bronson Medical Center, Kalamazoo, Mich.

Dr. Ernest William Eberling, The Clinic for Children, Starkville, Miss.

Dr. George Eckel Felknor, P.O. Box 29, Baytown, Tex.

Dr. Erwin D. Goldenberg, Kaiser Fontana Hospital, Fontana, Calif.

Dr. William Roy Green, 5601 Old Mission Rd., Chattanooga, Tenn.

Dr. Arnold E. Hauser, 820 Marin St., Vallejo, Calif.

Dr. William Carter Hawkins, 4325 Cole Ave., Dallas 5, Tex.

Dr. Jim Gilbert Hendrick, 910 North State St., Jackson, Miss.

Dr. Fontaine Sallis Hill, 20 South Dunlap, Memphis, Tenn.

Dr. LeRoy Edward Hoeck, 108 19th St., S.E., Apt. 1, Washington 3, D. C.

Dr. Joseph Gordon Holt, Jr., 306 Hamilton Bldg., Wichita Falls, Tex.

Dr. William Floyd Humphreys, Jr., 112 E. Third Court, Panama City, Fla.

Dr. Eloise Eberling Johnson, 314 Blakely Dr., San Antonio, Tex.

Dr. Frank Goulding Keller, 1023 Dauphin St., Mobile, Ala.

Dr. George Peyton Kelley, 224 Pennsylvania, Shreveport, La.

Dr. Frank Robert Kinberger, 547 Esplanade Ave., New Orleans, La.

Dr. Herbert W. Korngold, 2524 Jay St., Sacramento, Calif.

Dr. Joe L. Lipscomb, 904 W. 7th Ave., Amarillo, Tex.

Dr. Gertrude C. Luther, Commercial National Bank Bldg., Anniston, Ala.

Dr. Stephen Laurence Madey, 805 North Blvd., Baton Rouge, La.

Dr. Jerome S. Mark, 4418 Vineland, North Hollywood, Calif.

Dr. Jack F. McKemie, Moody Clinic, 1611 Fifth St., Corpus Christi, Tex.

Dr. Marion Smith McLellan, Jack Tar Court Hotel, Galveston, Tex.

Dr. A. Ziegler McPherson, Physicians and Surgeons Clinic, Yazoo City, Miss.

Dr. Bruce Baxter Newman, 4072 Hampton Ave., Western Springs, Ill.

Dr. Georgia B. Perkins, 4200 East 9th Ave., Denver, Colo.

Dr. Guy Eugene Rader, 817 East Central Ave., Albuquerque, N. M.

Dr. Stephen Wheeler Royce, Jr., 49 South Cataline St., Pasadena 1, Calif.

Dr. Lee H. Sanders, 627 West Jones St., Raleigh, N. C.

Dr. Herbert Victor Louis Sapper, 525 N.W. 11th St., Oklahoma City, Okla.

Dr. Alvis Joe Scull, Stanford University School of Medicine, Clay and Webster Sts., San Francisco 15, Calif.

Dr. Robert David Shuttee, 204 Bass Building, Enid, Okla.

Dr. Thomas Randolph Clinton Sisson, 35 Chittenden Ave., Crestwood (Tuckahoe 7), N. Y.

Dr. William Price Stepp, 376 South Bellevue, Memphis 4, Tenn.

Dr. Oscar Syme, 106 South Girard Ave., Albuquerque, N. M.

Dr. Carolynn Downs Talley, 1430 Tulane Ave., New Orleans, La.

Dr. Daniel Martin Thomas, Medical Arts Bldg., Oak Ridge, Tenn.

Dr. John W. Thompson, 27 Eighth St., N.E., Atlanta, Ga.

Dr. George Clifford Thorne, 607 West 14th St., Austin, Tex.

Dr. Steve H. Turnbull, Jr., 1255 Eastmoreland, Memphis, Tenn.

Dr. John B. Welsh, 931 Meridian St., Anderson, Ind.

Dr. Lloyd Parrish Williams, 110 N. Durkee St., Appleton, Wis.

The **American Board of Pediatrics** announces the following dates for oral examinations:

Atlantic City, N. J., May 5, 6, and 7, 1951.

Detroit, Mich., June 8, 9, and 10, 1951. This examination session replaces the one originally scheduled for Cleveland in June.

The 75th annual meeting of the **American Association on Mental Deficiency** will be held at the Hotel New Yorker in New York City on May 23 through 26, 1951. The organization is comprised of medical, educational, psychological, and other authorities professionally concerned with mental deficiency. According to estimates of the association, 7 per cent of the population of the United States is afflicted with some degree of mental retardation because of brain impairment.

A postgraduate pediatric course for general practitioners will be given at the **University of Arkansas School of Medicine,** Little Rock, Ark., by the Pediatric Department, May 14 and 15, 1951. Dr. Myron E. Wegman, of Louisiana State University Medical School, New Orleans, La., and Dr. Gilbert B. Forbes, of Southwestern Medical School, Dallas, Texas, will be the guest speakers. No fee will be charged for this course.

The **Cook County Graduate School of Medicine** announces a two-week Course in Cerebral Palsy, by M. A. Perlstein, M.D., and Associates, July 9 to July 21, 1951. This is an intensive didactic and clinical course in Cerebral Palsy intended primarily for physicians working with such children. All communications regarding this course should be addressed to the Cook County Graduate School of Medicine, 427 South Honore St., Chicago 12, Ill.

Pediatric Consultant is wanted for a nine-bed Chronic Disease Ward operated by the Alaska Department of Health. Consultant also extends consultative service to the private physicians throughout Territory. Starting salary $9,300; 38-hour week; one month vacation; in-service training. Applicant must have two years' graduate study and two years' experience equivalent to American Board requirement. For complete information write Dr. C. Earl Albrecht, Commissioner of Health, P. O. Box 1931, Juneau, Alaska.

Editor's Column

RESEARCH

PERHAPS the most frequently heard word in connection with medicine is research. Its ultimate derivation is from the Latin *re* (again) + *circare* (to go around). It is variously defined as a careful inquiry or investigation; the effort to find new information by investigation or through investigation of the sources; and investigation to discover facts by study. It is a noun and hence the expression "medical research" is correct and the frequently used expression "research medicine" incorrect usage of the word. No one in this day or generation needs to defend the importance of research in medicine or in any branch of science. It is and has been the basis of all progress in the medical sciences and arts.

But all research is not of equal importance or value despite the fact that seemingly unimportant observations have many times led to the most important scientific developments. Nor is medical research a thing that is limited or confined to the laboratory, as some are inclined to consider. Some of the most important advances have come from purely clinical observation.

In a recent address, McKhann has defined four categories of research in clinical medicine which he ranks in importance from low to high. While undoubtedly there will be some who will disagree with the order of their importance, the four categories adequately define the types into which medical research may be divided.

"I. Lowest is educational or review research which should not merit even the name research but which brings together, often quite uncritically, the published data on some subject of interest to the worker.

"II. Second up the scale is appraisal research in which work or ideas of others are analyzed to be confirmed or refuted. By far the largest volume of research in clinical departments falls into this category. While appraisal research is an essential activity of a clinical department since the changes in care of patients are based upon it, no department can become outstanding that does not go beyond efforts of this type.

"III. Third up the scale is the case report type of research in which unusual features of a case are observed and reported. This category is placed above appraisal research because it may lead to some thinking by the worker about the causes of the unusual finding and further progress.

"IV. Highest in the list and often stimulated by and a corollary of the third type is initiatory research. As a result of observations in the clinic or laboratory and arising from correlation and integration of these observations come ideas that lead to positive advances in medicine. Yet it is seldom that the first forward steps in a field do more than point the way to further work that in many instances rapidly supplants the first steps or may even disprove the first steps. The initiatory work, however, has opened the field and made the further progress possible."